Volume VI No. 1

THE

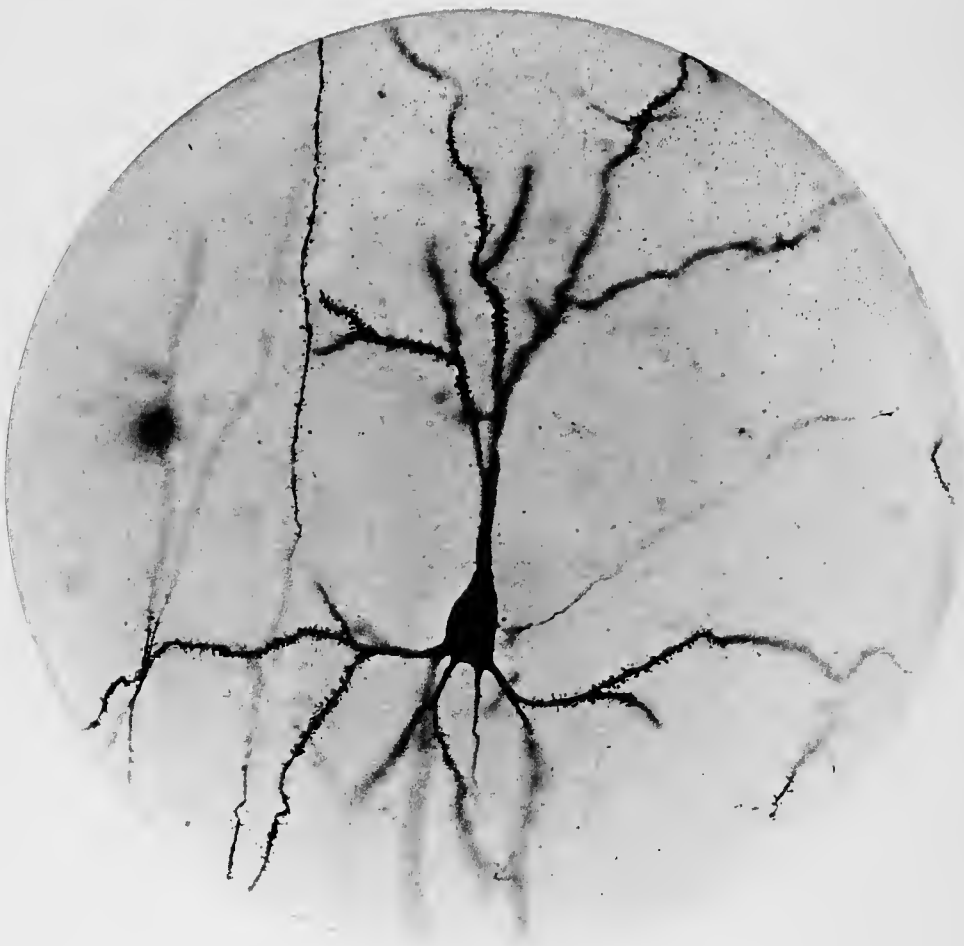
JOHNS HOPKINS HOSPITAL REPORTS

REPORT IN NEUROLOGY, III

By Henry J. Berkley, M. D.

CONTENTS.

BALTIMORE
The Johns Hopkins Press
1896



FRONTISPIECE I.

NORMAL PYRAMIDAL CELL. GUINEA PIG. X 550.

PHOTO. BY DR. A. D. HOEN. PRINTED BY A. HOEN & CO.

FRONTISPIECE II.

NORMAL PURKINJE CELL. HUMAN BEING. X 275.

PHOTO. BY DR. A. O. HOEN.

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NOTE.

The words Neurôn, Neurodendrôn, Neuraxôn, and their abbreviations, should be spelled with the circumflex accent throughout these articles, and, together with Neurodendrite, have the original significance given them by Waldeyer and Koelliker.

STUDIES ON THE LESIONS PRODUCED BY THE ACTION OF CERTAIN POISONS ON THE CORTICAL NERVE CELL.

Introductory. Recent Literature on the Pathology of Diseases of the Brain by the Chromate of Silver Methods.

The amplification of our knowledge of the minute anatomy of the nervous system has taken such tremendous strides during the past few years that an insight into the recent advances has already become widely known, not only among those who make an especial study of this branch of anatomy, but to every one interested in the progress of the science of medicine.

This increased accuracy in our information has been owing almost entirely to the chromate of silver method introduced by Golgi and his followers, aided in a measure by the vital methylene blue stain of Ehrlich and the methods of Nissl.

Information concerning the pathological changes in the central nervous system, more particularly in the cortex of the cerebrum, has not, however, kept pace with the study of its histology; experimental research, only by which an accurate understanding of human pathological lesions can be drawn, has not been accurately followed, and to-day we stand at a point not greatly advanced over that at the beginning of this decennary. Especially is this true of the cerebral lesions induced by infectious diseases, where changes are supposed, but their character remains almost unknown.

The one great reason for the lack of progress in this direction has been owing to the few stains from which any accurate return could be expected. It is true that methods have again and again been devised, only to be discarded within a few years as untrustworthy, and by which two observers could seldom see the same structural lesions.

Two different and entirely opposite methods, that were first used for histological purposes, have lately claimed considerable

attention. The method of Nissl offers a field for study that is in a measure accurate and reliable, but the variety of cellular changes shown by it are ofttimes difficult of interpretation, though the main objection is that while it allows of a fair view of the protoplasm of the body of the nerve cell, the distal portions of the cell, the dendrites and their appendages, are invisible, and likewise the important axis cylinder remains untinged.

The other method, the silver stain, while it impregnates all portions of the neuron, has many objections. The nerve elements are not certainly stained, and it permits little information to be gathered of the variations in the structure of the protoplasm.

Investigators with the Golgi method have all been hampered with the infrequency and imperfect staining of the nerve elements in adult tissues and the general difficulties attending the examination of human pathological material, as well as by the deficiencies in our knowledge of post-mortem changes likely to be met with in these specimens.

I believe the first application of the Golgi silver method in pathology was made by Kronthal in 1887 (Neurol. Centralblatt) on a brain from a case of general paresis, and as his results did not seem to be encouraging, the further use of the method seems to have been abandoned for the time. In 1892-3, in the course of other work, I made several attempts to study the brains of alcoholics and paretic dements, but with indefinite and unsatisfactory results.

During 1893, Greppin (Arch. f. Psych., Bd. 24) renewed the attempt to discover definite lesions in the brains of paretics, but also with imperfect issue.

During 1894 several memorials on similar subjects appeared, modifications and improvements in the process of impregnation having been made in the meanwhile. Colella (Sulla fine alterazione della cortecia cerebrale in alcune malattie mentale, Roma, 1894) studied the cerebra in several cases of general paralysis and alcoholic psychoses with somewhat better success, in that he found well-defined changes, both in the dendrons and axons of the cells, that were in part afterwards substantiated by other observers; the alterations being mainly in the form of tumefactions of these portions of the neuron.

Next in order follows the well known work of Golgi (Berl. klin.

Woch., No. 14, 1894) on the pathology of experimental rabies. Here the prevailing lesions were on the same order as those seen by Colella in paresis, namely, a varicose condition of the axons and neurons; but they extend further, as Golgi finds and depicts atrophic degenerations in the corpora of the nerve cells.

Following the article of Golgi came one by Klippel and Azoulay (Arch. de Neurologie, 1894) on the alterations of general paralysis, the lesions found being of the same character as those previously determined by Colella, but their interpretation of the tumefactions of the dendrites, when they describe that the first stage of the process consists of an abrasion of the spines (gemmulæ) covering the protoplasmic expansions, then an agglutination of many spines to form irregular bands of protoplasm, and finally a coalescence of these drops to form larger ones upon the dendritic stem, is certainly erroneous, for, as we shall presently see, the gemmulæ have no part in the process beyond rapid atrophic changes.

In the fall of the same year appeared the contribution of Andriezen (Brain) entitled "Newer Aspects of the Pathology of Insanity," in which there is a short paragraph on the lesions in alcoholic insanity, where a process analogous to that mentioned by Colella and Klippel is figured and described, but Andriezen finds much greater implication of the corpora of the cells than the former writers.

This short sketch of the literature finishes all the pathological work up to the beginning of the present year, and, it will be observed, includes only one experimental study.

In March, 1895, Monti of Pavia (Bollet. della Soc. Med.-chir. di Pavia, March, 1895) published a monograph on the changes found in the cerebral cells after the induction of artificial embolism by the injection into the carotid artery of the dog of lycopodium or carbon powder. The results obtained were exceedingly interesting and instructive, and the drawings accompanying the paper were made with greater care and accuracy than in any of his predecessors' works.

Briefly, he finds, following the injection of the powder, that after an interval of at least five hours has elapsed there begins in the protoplasmic extensions of the nerve cells an alteration limited to the divisions that come off from the main stems at some distance

from the cell body, the amount and intensity of the pathological alteration depending on the length of time after the injection. There may be in these cases only a lesion manifest in the branch or branches turned toward the site of the nearest embolism, while in others more clearly within the area in which the blood supply has been cut off, complete implication of every extension of the cell is seen. The changes in the earlier instances consist of an irregular swelling of the protoplasmic substance of the dendrite, and commence always at the distal extremity of the cell and proceed toward the centre. The axon is involved only subsequently to the degeneration of the cell's corpus. Monti applies the name " varicose atrophy " to this peculiar condition.

Quite as interesting as the preceding study is another by the same writer on the alterations produced in the central nervous system by *starvation*. Though the lesions of the nerve dendrons are of a somewhat different order than those before described, they yet bear the same imprint. The cerebral cells show great thinning of all the dendrons of the involved cells, very small varicose enlargements form along both apical and basal dendrites without implication of the cell body or axon.

The last article completes the entire literature on the pathology of the several morbid conditions as seen with the chrome-silver methods, besides my own investigations, which have been accomplished by a somewhat different stain, and comprise, besides the present studies, some work on the pathology of mental diseases, part of which has been published and part remains incomplete.

Substantially we have found lesions of the nerve cell structures in the form of parenchymatous degenerations, both of the protoplasmic extensions and corpora of the nerve cells, but no involvement of the axis cylinder, except in exceptional instances, and this in all the morbid processes investigated.

One point we would call attention to before closing this portion of the paper, the fact that no matter how extensive and diffused the destruction may be among the cells of the cortex, a number of the elements remain histologically sound, which would seem to indicate that certain neurons of a brain-rind have a higher degree of resistance to destructive influences than their fellows; and this fact is not without its importance in the consideration of mental

diseases, especially those caused by the poisonous products of certain pathogenic bacteria.

I should also state that none of my work has been done with the ordinary rapid Golgi method, which we have found entirely unsuitable and unreliable with adult tissues, but with the silver phospho-molybdate method, which offers greater advantages, both in the fineness of details and certainty of staining over the other.

While the study of the lesions of the nervous system by silver methods has thus disclosed a number of pathological conditions, work has not been entirely wanting in the experimental field by the Nissl methods. Time does not permit me now to go into details, and I would refer those interested to the recent articles of Sarbo (Neurol. Centralblatt, Aug., 1895) and Dehio (Centralblatt f. Nervenheilkunde u. Psych., March, 1895), also to the work now being done in Nissl's laboratory on cell changes following the extirpation of muscles (Centralblatt f. Nervenheilk. u. Psych., 1894).

PART I.—ALCOHOL POISONING.

SECTION I.—EXPERIMENTAL LESIONS PRODUCED BY THE ACTION OF ABSOLUTE ETHYL ALCOHOL ON THE NERVE CELLS OF THE RABBIT'S BRAIN (CHRONIC ALCOHOLIC POISONING).

The most extensive treatise on the pathology of chronic alcoholism to be found in the English language is Bevan Lewis' article in his text-book on Mental Diseases. Indeed, so widely has it been accepted as the minute anatomy of this morbid state, that in Tuke's Dictionary of Psychological Medicine it is quoted to the exclusion of all other writers. Abstracted, it reads as follows: The changes in the vessels are nuclear proliferation, atheroma, and aneurismal dilatation, the last eventually giving rise to a cribiform condition. The motor cells are swollen and rounded, stain deeply, become granularly pigmented, and the apical processes degenerate. The cellular wall is thickened. There is a considerable quantity of pigment deposited between the shrinking protoplasm and this cell wall. The processes of the cells are stunted and covered with nuclei, and the protoplasm is granular or vacuolated.

In the lowest layer the scavenger cells and nuclei cover the spindle nerve cells, which are very much degenerated and altered, and are practically being devoured by these proliferating cells.

The medullary sheath of the nerve processes gradually disappears, or is so altered by the invading connective tissue that the axis cylinder—which is frequently fusiform, as in other cases of inflammation of the nerve fibre—can be perfectly well stained with the aniline color, when it becomes a prominent feature in the cortex. Lewis describes the motor cells of the so-called third layer as being the first ones implicated in the cortex, and that those of the deeper and more superficial layers follow in order.

It would seem from this description as if there were no specific lesions of the nervous system from the continued abuse of alcohol to be discovered; certainly the vascular changes found are frequent in brains that have exhibited no clinical picture of the

effects of alcohol during life, and taking atheroma and miliary aneurisms from among the list, it would seem as if there were other conditions of which we at present know nothing, as all pathologists are familiar with brains that show in marked degree these changes, and whose owners have been in nowise addicted to the use of the drug. Nevertheless there can be no doubt that alcohol in the common forms of wines and distilled liquors does exercise a direct influence on the cerebral vessels, irritating their coats, especially the intima, perhaps, paralyzing the functions of the muscularis in more or less enduring fashion, hence giving rise—from the irritation—to nuclear proliferation, and from the distension of the vessels to transudations, local minute extravasations, clumps of hematoidin granules and detritus in the perivascular sheaths, then blocking of the lymph currents, and general disturbance of the lymph flow in the perivascular and pericellular channels.

Of the changes in the nerve cell produced by the direct contact of the diluted drug flowing with the nutrient serum from the blood channels into the pericellular spaces, we at present know nothing, but from a clinical standpoint the immediate effect in occasioning disturbed metabolism must be very great.

With Lewis' ideas of the coarser changes produced by the long-continued abuse of the poison we are in unison, as only too frequently in alcoholic brains have we met with the shrunken protoplasm, stunted processes, and granular cell bodies; but these alterations mark only the after-effects of long-continued malnutrition and irritation of the cells. In other words, we see only the late effects of a degeneration which has proceeded a considerable distance toward utter deterioration before it is visible to carmine, hematoxylin, aniline blue-black, and freezing methods. What we really wish to ascertain is not only the condition of the protoplasmic body, but also the early changes in the finest twigs of the dendrites, and the finest variations of the nucleus and nucleolus from the normal.

A newer, though very small, literature has sprung up since 1890, when the work of Bevan Lewis first appeared, and the methods of histological research have been extended to a realm whose boundaries were only beginning to be entered upon at

that date. I refer to the commencement of the extended use of the chromate of silver methods, and the magenta and methyl blue stains of Nissl, the one almost fully supplementing the other in so far that by one we may obtain perfect impregnations of the neuron to the uttermost limits of the dendrites, and by the other an accurate view of the condition of the cellular protoplasm, and in particular the nucleus with its chromophile particles.

The newer literature, as already mentioned, is very scant; portions of only three articles treat of the lesions of the nerve cell when subjected to the presence of alcohol in the living organism.

Colella (Arch. ital. de Biologie, 1894, p. 216, and Fine alterazione della corteccia cerebrale, Roma, 1894), by the application of the Golgi silver method to the cortex of an alcoholic brain, found lesions of the neuraxon of the nerve cell, and slight involvement of the cell body and dendrites in the alteration. He speaks of the blood-vessels and neuroglia as not being implicated in the change.

Vas (Arch. f. exper. Path. u. Pharmakologie, Bd. XXXIII, p. 141), in an experimental work on the poisonous effects of alcohol and nicotine on the nerve cells, finds well-marked changes in these bodies, especially in the great cells of the anterior horns of the spinal cord, and in the spinal and sympathetic ganglia. As a first change the cells lose their chromatin structure, the finely granular appearance is perceptibly diminished and gives place to a homogeneous swelling. In advanced cases of the alteration, the cellular protoplasm alters its power of taking up the coloring matter and appears darker than normal. A shrinking of the protoplasmic body cannot be definitely ascertained.

The study of Andriezen (Brain, 1894) is of equal interest with the foregoing works, and is worthy of careful consideration. Using a modification of the Golgi method, he finds extensive changes in the neurodendrites and neuraxons of the nerve cells of the human cortex; the "alteration beginning in the fine bead-like contact-granules" upon the substance of the protoplasmic extensions, proceeds to moniliform swellings along the course of the protoplasmic twigs. With the further progress of the lesion these softened and enlarged protoplasmic masses form irregular botroidal masses, mainly clothing the now irregularly bared protoplasmic stem, which

rapidly becomes attenuated. "The changes in the cell body are of similar nature, and consist in a gradual disintegration after the apical and others of the processes have suffered. Here and there, at the side of the cell body, the protoplasm seems to become frayed, or, as it were, eroded. In other cases the cell protoplasm becomes vacuolated from within, and the process continues until the whole interior protoplasmic structure is channeled by holes and seams of liquefaction."

The nerve fibres of the cortex Andriezen finds granular and wrinkled in outline, and what is even less certain, a process of unequal staining, portions of the filament being completely stained, while other portions are pale or colorless, and only visible to the highest powers of the microscope.

It will be noticed that in none of these articles is there any mention of the state of the nucleus and nucleolus. This partly arises from the methods of staining used in the various investigations. Lewis' aniline blue-black does not allow of the interior structure of the cell to be accurately seen, nor does the silver method permit any inquiry in this direction; and Vas, who used nuclear stains, does not seem to have considered the nucleus of the nerve cell, probably from the difficulties that attend its accurate investigation.

The tissues at our command have, however, allowed of more accurate procedure, and in this direction my studies have been partly directed, somewhat to the exclusion of the intimate structure of the nerve cell's protoplasm.

My anatomical material, owing to the kindness of Prof. Welch and Dr. Friedenwald in furnishing me with the brains of a number of rabbits that had been subjected to the continued—*intra vitam*—action of absolute ethyl alcohol over a considerable space of time, allowed me a better opportunity for the investigation of the nerve cells than could be obtained from human alcoholic brains, in so far that we had an accurate knowledge of the amount of alcohol the animal had been subjected to per kilo of bodily weight, and the duration of the alcoholic poisoning, and last, though not least, we are enabled to obtain the cerebra in much fresher condition than can be had from the autopsy table.

Appended is a condensed table of the histories of the five rabbits used.

CONDENSED RABBIT HISTORIES.

No. in Series.	Apparent Age.	Quantity of Alcohol fed per diem.	Began to feed.	Died.	Weight at time of death.	Clinical cause of death.	Gross anatomical lesions found.	Weight at begin. of Exper. in grammes.
6	Adult.	5 to 8 cc.	Dec. 19, 1893.	Dec. 20, 1894.	1420	Convulsions.	Fatty heart.	1450
10	"	"	Dec. 30, 1893.	Oct. 27, 1894.	2500	Ascites.	Cirrhosis of liver.	1920
39	"	"	July 5, 1894.	Dec. 5, 1894.	1400	Convulsions.	Fatty heart.	1540
41	"	"	July 5, 1894.	Feb. 4, 1895.	1420	"	" "	1890
42	"	"	July 5, 1894.	Feb. 10, 1895.	1640	"	" "	1940

METHODS OF EXAMINATION.

All the specimens of brain tissue that came into my hands for the purposes of the study—pathological and normal—were hardened either in absolute alcohol or in Müller's fluid. For the Nissl method and modifications thereof, used for the demonstration of the cellular structures, and for hematoxylin-eosin staining for the blood-vessels, the former method of hardening was applicable; but for studying the finer dendrites of the nerve cells it became necessary to devise some ready method of staining by which impregnation with metallic salts could be obtained. Some research among the literature devoted to microscopic technique failed to afford any suitable process, and after consideration, the following method was adopted, and found to be more satisfactory than any other, and indeed gave more complete as well as finer pictures of the cortical neurons than the ordinary Golgi methods; and, though we have at the time of writing stained a large number of pieces of brain substance, we have yet to record a single failure in the process, though of course all the impregnations were not equally good. The great advantage that accrues to the pathologist from being able to make use of any desired portion of an entire brain hardened after the usual method in Müller's fluid is at once apparent, particularly when the impregnations obtained are much finer

than those had after a very troublesome and particular hardening process; and though it is a small consideration, it is more economical of osmic acid than the Cajal process, as the osmic acid mixture may be used more than once.

The staining obtained is much more intense than is found after the ordinary chrome-silver stain, the cell bodies and processes are jet black, and not even at the points of the finest dendrites does the familiar reddish-black color make its appearance.

The process is as follows: The cerebra are hardened in Müller's fluid until the tissue is of sufficient consistency to admit of fairly thin sections, which should not require more than two weeks at the room temperature. The portions of the brain selected are then cut into pieces, not more than three millimetres in thickness, and the selected portions then immersed in a mixture of 3% solution bichromate potass. 100 parts, osmic acid solution 1%, 30 parts. In this mixture the specimens lie from two to three days, are removed from the fluid and slightly dried on filter paper to remove any superfluous bichromate salt; are washed for a few moments in a weak solution of silver nitrate, and then go into the second mixture, which is made by adding two drops of phospho-molybdic acid of 10% strength to each sixty cc. of 1% arg. nitrate solution in distilled water.

The second mixture is only to be made as needed, and at the moment before placing the brain tissue in it. In the mixture of phospho-molybdate of silver in the free nitrate solution the tissues are immersed and allowed to remain without disturbance for two or three days, or, if it is not convenient to cut them at that time, a few drops of fresh silver solution of the same strength may be added to the old fluid, and in this the tissues may remain indefinitely. The object in adding the additional silver nitrate is to prevent any chance of all the salt being precipitated, as plain water will soon cause a deterioration of the distinctness of the impregnation of the nerve and neuroglia cells. Light does not seemingly affect the process unfavorably, nevertheless it is better to keep the jars containing all the mixtures from the direct rays of light. I have found in the winter season that it is necessary to keep both the bichromate and silver mixtures at a uniform temperature of about 25° C.; if the temperature be lower there is

liability that a deposit of coarse precipitate will form along the outer margin of the specimens, but if the bottles are kept at a much higher temperature no good impregnations can be obtained and a dense fine precipitate is found throughout the slides.

The individual details of the component parts of the neuron are finer than in the Golgi sections; each element stands out clearly and distinctly, the axons and their collaterals are clear and not too numerously tinged, and the gemmulæ or buds on the protoplasmic processes are fully and equally impregnated and appear in their proper relations to the parent dendrite. There is occasionally some coarse precipitate along the edges of the section, but rarely the finer one that is so annoying in the older chrome-silver specimens.

Histology of the Normal Rabbit Cortical Cell by Nissl's Method.

The first part of the study was conducted on the brains of two rabbits, hardened in absolute alcohol and stained according to the methods of Nissl, and with eosin-hematoxylin.

In order to fully appreciate the structure of the nerve cell stained by Nissl's method we must first glance at the normal nerve cell as seen in control preparations. The aniline dye does not impregnate all portions of the cellular protoplasm equally, but leaves clear spaces between others more deeply stained—the chromophilic particles. In the cell body the arrangement of these chromophilic particles is always definite, though varying considerably in their disposition according to the character of the cell itself. Thus in the cells of the anterior horns of the spinal cord we find a net-like arrangement of the stained particles (arkyochromic cells), while those of the cerebral cortex have them mainly arranged in rows (stichochromic cells). Furthermore, these various cells are divided into several main groups by the different relations of the nucleus to the cellular protoplasm. Only two of these groups are ordinarily to be seen in the cortex: (1) cytochromic cells, or nerve bodies having a nucleus approximately the size of a leucocyte, and with a very small amount of stained protoplasm surrounding it; and (2) somatochromic cells, having a nucleus of moderate size which is surrounded by a considerable body of protoplasmic substance having a definite contour.

With the cytochromic cells we have but little interest, the main body of the cortical cells being somatochromic and of the stichochromic variety.

Furthermore, the nuclei present variations in their size, contents, refraction, and receptivity to the absorption of aniline dyes. The arrangement of the contents of the nucleus also varies considerably. In some we find only a single well defined nucleolus, the edges smooth and rounded, surrounded by very fine dust-like grains, all deeply stained by the dye, the whole imbedded in a transparent nuclear substance that does not take up any of the aniline. Others have two or three nucleolar particles—seldom more than this number—all smooth, and situated in the several quarters of the nuclear circle, imbedded amidst dust-like grains of a finer or coarser appearance. Besides these chief varieties a third is rarely present, in which the nucleus is less distinct than in the others and the nuclear dust is somewhat coarser than in the other varieties. All these forms present little difference in their staining qualities, the amount of dye taken up outside the nucleoli and dust is very small, and the nucleus in consequence is invariably quite refractile and light colored. The fourth variety of nucleus is differentiated by the variation in the receptivity to the staining fluid. It absorbs a little more of the dye, sufficient to color it slightly, but the number of these cells in the healthy brain is minimal, and for the practical examination they may be excluded.

Pathological Histology of the Absolute Alcohol Specimens.

The two rabbits of this series have to be considered separately on account of slight anatomical differences.

The capillaries and intermediary vessels in the control specimens have a smooth regular outline, the nuclei in the walls are sharply stained, take up an equal quantity of the coloring matter, and the cell structure between the nuclear points is free from a suspicion of color (eosin sections do, however, have a slight tingeing of the capillary wall with the dye). The perivascular spaces are narrow but distinct, and hold no debris of any kind.

In rabbit No. 10 the smallest arteries have an altogether different appearance from the control preparations. The walls of many

of them are irregularly shrunken, at intervals almost botroidal in appearance; and the nuclei of the vascular walls, while not increased in numbers, are swollen, absorb more of the aniline dye, and project considerably into the lumen of the canal. The perivascular space is larger than in the control preparations, and the hyaline membrane separating it from the cerebral substance is a little more definite than normal. As we progress upward in the scale of size the changes of a pathological character do not increase greatly, except in so far that as the vascular walls become thicker the irregularity in their boundaries is gradually lost, while on the other hand the nuclei, especially those of the outer layer of the vessel, are somewhat multiplied, at times, though rarely sufficiently so to cover the exterior of the vessel with dense aggregations of round nuclei, through which the proper structure of the canal is seen with difficulty. The perivascular spaces around these nucleated vessels are larger than usual, and the cerebral edge of the space stains more deeply than normal. Occasionally there are a few grains of hematoidin debris and fine granular matter within the space, more commonly it is vacant. On transverse section the walls of the vessel appear to be a little thickened, the lumen narrowed, the change affecting the intima more than the media. Very few of the arteries show any very pronounced changes. Four or five miliary hemorrhages into the sheaths of small vessels were noted in the several sections, all near the pial margin. Altogether no very definite lesions could be determined in the blood-vessels.

In rabbit No. 10 the vast majority of the nuclei of the somatochrome cells of the cortex show alterations and departures from the standard established in our control preparations. The most prominent of these changes lies in the central nucleolar figure, for in the place of the smoothly appearing dot, in or near the centre of the nucleus, it now appears roughened, spongy, or even with elongated projections from its surface (compare photos. Nos. 1 and 2). Not only is the nucleolus roughened, but it is also considerably enlarged, occupying now from an eighth to a sixth of the interior of the nucleus, its projections extending to the periphery of the circle. Around these nucleolar figures is grouped a small amount of nuclear dust particles resembling an irregular circle, but the remaining portions of the nucleus are now

comparatively free from the presence of molecular particles, i contrast to the control preparations. In the clear karyoplasr there is a decided tendency to take up more of the aniline stain so marked does this tendency become at times that the content of the nucleus are rendered indistinct, and the body is much les refractile than normally.

The above description applies exclusively to the mononucleola variety of nuclei. The varieties showing two or more nuclei hav nearly disappeared, and it is highly probable that the largest masse of spongy nucleoli in the altered nuclei are formed by an agglut nation of these chromophile masses; for, indeed, in not a few c the cells enlarged and swollen nucleolar particles are seen approacl ing each other in some portion of the nucleus.

Hardly any nuclei are found differing from these two pathc logical varieties, though a not inconsiderable number of the no: mally disposed nuclei are seen here and there in the field, th proportion, however, being inconsiderable.

To recapitulate, we find alterations of the nuclei chiefly in th disposition, swelling, and irregularity of contour of the nucleol chromophilic particles.

Rabbit No. 39.—The blood-vessels show the same condition a in No. 10, only not so accentuated. The botroidal appearance not so marked. The nuclei of the intermediary vessels are mult plied to some extent, an alteration that extends into the smalle veins. In one small vessel I detected a distinct aneurismal dil tation. All the nerve cells take up a larger quantity of the anilir dye than usual, the chromophile particles in the protoplasm are n so distinct, the nuclei are nearly all mononucleolar, and the nucle substance stains a deeper hue than in the control. The nucleo are comparatively seldom enlarged or swollen, here and there or is seen—perhaps an average of one in fifteen cells—but in mar others there is a tendency to be out of proportion in size the surrounding ones. The nuclear molecules are fine, while th substance itself takes up an unusual amount of the dye.

A few sections of the cortex of this rabbit were stained by th Weigert method, but I could detect no variation from the norm among the fibres of the coarser bundles of nerve filaments. Th finer intercellular fibres are not very numerously stained.

The Normal Structure of the Rabbit's Cortex as seen with the Silver Phospho-Molybdate Stain.

The arrangement of the nerve cells in the cortex of the rabbit's brain differs little from that of other mammals. The structure consists of three indistinct layers of cells with beneath them the medullated masses of white matter. Viewed with low power, there is but one distinct cellular layer.

In the outer or molecular lamina are situated a minimal number of small irregular nerve cells, whose axis-cylinder processes course parallel with the surface of the brain. Beneath this region lie small pyramidal, elliptical, and irregular cells, their axons always turning downward. Beneath these cells lie others of approximately pyramidal form, but of a larger size than those immediately superjacent to them, and mingled among these are a few irregular cells. All the neuraxons from this region turn downward into the radial bands of fibres. The apical dendrites of all the pyramidal cells reach nearly to the pial limit, and by division form an intricate meshwork of protoplasmic extensions beneath it. The dendrites of the irregular cells spread out laterally to a greater extent than vertically, but without definite course.

Beneath the large pyramidal cells and bordering on the white medullated fibre-layer lie cells of several different forms, mainly irregular pyramidal and angular. The stronger processes of these cells are upturned, while the axons are downturned. Lying between these cells, and far more numerous, are small irregular cells with protoplasmic extensions outstretched in all directions. Their neuraxons are all turned toward the surface of the brain, and on their way thither they give off rather numerous collaterals, and finally reach the tangential band along the pial surface, among whose fibres they are eventually lost. Golgi intermediary cells are scattered through the lower two layers.

All the pyramidal cells of the cortex of whatever kind, and very many of the irregular and angular ones, have coming off from their protoplasmic processes short rectangular projections or gemmulæ, that have been so universally found by the silver stain in the brains of all animals as not to admit of the possibility of a doubt that they are present during life, and are not simple artifacts, and indeed they have been demonstrated in particularly fine

Nissl preparations (Lenhossék), and are undoubtedly a factor of considerable importance in the economy of the nerve cell, as they must without doubt come into contiguity with the terminal endings of all classes of nerve fibres of the cortex. On the apical processes of the pyramidal cells the gemmulæ are usually pin-shaped straight projections on the process, terminating in a bead-like ending. Higher up they lengthen out and show the universal presence of the spherical ending more distinctly. On the thinner branches of the cells, especially those that come off from the basal extremity, they are longer, thinner, and arranged with considerable regularity, and give to these dendrites something of a feathered appearance.

Besides the gemmulæ, the nerve cells have on their branches a small though variable number of varicosities. On the thicker portion of the apical processes these varicosities are never present, but on the thinner dendrites they are here and there to be met with, particularly at the branchings of the stems. These varicosities must be held to be normal, as they are to be demonstrated in methylene blue as well as in silver preparations.

With the Purkinje cells of the cerebellum, the gemmulæ contribute greatly to the actual outspread of the dendrons. They are arranged with great regularity, and endow the extensions with more of a feathered appearance than those of the cerebrum. Knots upon the stems of the extensions of the Purkinje cells are present, and give them an uneven appearance.

Along the outer edge of the cortex numerous forms of support neuroglia cells, such as have been described by Retzius and others, are seen; but lower, among the nerve cells, the glia elements are but sparingly stained. Few of these belong to the long-rayed Golgi type, but are replaced by a cell with quite large body, and short but thick and knotty arms. These cells are always to be found in the immediate vicinity of an intermediary blood-vessel, which they frequently surround, and send off to its hyaline sheath one or more thickened processes that terminate in knob-like endings. In disease, unlike some other varieties of neuroglia cells, they atrophy and disappear.

Pathological Histology of the Rabbit's Cortex in Chronic Alcoholism as seen with the Silver Phospho-Molybdate Stain.

The material for this portion of the study comprised the brains of three rabbits preserved in Müller's fluid. The results obtained from all the rabbits were similar. In formulating any description of the lesions of chronic alcoholism we should always have prominently before our mental vision the fact that the normal characteristics of the cortical cells, as we see them by any of the more usual methods of preparation, vary within certain fixed limits, and that these must be overstepped before one can say with certainty that we have before us a pathological condition. By any mode of staining with chrome-silver salts this is, perhaps, more strikingly the case than by other methods, and the observer must be constantly upon his guard against deceptions into which he may very innocently fall.

A portion of the uncertainty of the silver method we have been able to obviate by the fact that the new method of staining we have pursued is more fixed and reliable than any other treatment we have hitherto tried. Truly a comparison of many hundreds of normal cells in the control preparations shows little or no variations in the cells beyond those inherent to the several varieties.

The intrinsic variations in the formation of the neuron are, for the practical purposes of this examination, reduced to the normal inequalities or varicosities in the construction of the dendrons. These inequalities in the cortical dendron are, as before stated, of comparatively infrequent occurrence in contrast to those of certain of the cells of the basal ganglia, and belong either to the finer dendrites of the irregular cells, or to the points of division of the dendrites, and are then usually of triangular form and small size, and may be readily excluded in an examination for pathological lesions. Besides the swellings in the course of the dendrons, we must always be on the watch to exclude certain processes of the support neuroglia cells that traverse long distances of the cortex and exhibit a pearl-string swelling in the course of the fibre. These nodal formations lie at perfectly regular distances from one another, and present the appearance of a double cone

of small size. It is, of course, only when these fibres are detached from the cell body that they can give occasion to error. Another source of trouble to the observer is the occasional deposit of rounded masses of precipitated silver upon the dendrons, or upon the cell body, but this may usually be cleared away without difficulty by a careful examination of the edges of the questionable mass with strong transmitted light, when the irregular structure of the precipitate and serrated edges will at once appear. Still another source of error is the fracturing of the protoplasmic processes by the edge of the knife in cutting the sections, the chrome salt rendering the protoplasm brittle; but once aware of the difficulty, it is easy to eliminate it as a source of error.

After all possible allowances have been made for artifacts and physiological variations from the normal, as well as inequalities in the staining process, there remain a large number of cells in our alcoholic brains that are distinctly abnormal. The principal lesions in them, to which we would call attention, are a distinct diminution in size, a shrinkage of a vast majority of all the cortical cells, particularly in the outspread of the branches, certain swellings of the dendritic processes with disappearance of the gemmulæ, and roughening of the stronger processes, and to a less extent of the cell body.

We have not succeeded in staining the Cajal cells satisfactorily in the alcoholic rabbit's brain, but with this exception the cortical cells of all layers may in chronic alcoholism be considered to be involved in a process of retrogressive metamorphosis; some in greater, some in less degree, but all are implicated to some extent. The small cells of the outer layer show degenerative changes, the pyramidal cells show the same in greater intensity, the lowermost pyramidal and irregular cells are equally involved. Fortunately, the pyramidal cells, from their very fixed character and larger size, are more easily studied than the others, and our principal attention has been directed to them.

It is extremely difficult to determine in the silver preparations the approximate proportion of cells that are normal and cells that may definitely be held to be abnormal, from the fact that but an extremely small proportion of the total number of cells in all the layers is at any one time stained. In some of the preparations

from the same brain but one in a dozen cells show any definite change, while in other sections nearly all the cells are altered. It would, perhaps, be safe to conclude that one out of every three or four nerve elements, in the brains of the three alcoholic rabbits we examined, showed departures from the normal in some form, though the percentage is probably higher. Another source of error in estimating the numbers of diseased cells arises from the circumstance that we can form no idea whether the silver salt preferably impregnates the normal or abnormal cells, for even in histological preparations no one has advanced any plausible theory why the silver elects here and there a cell to impregnate and leaves the others perfectly untouched by the salt. The impression conveyed by an examination of a long series of sections is that the action of the silver is preferably confined to the normal cell. Golgi (Berl. Klin. Wochen., No. 14, 1894) opened this question as to the capability of the diseased cell receiving the silver stain, but could only answer it to the extent that even much degenerated cells were impregnated.

A careful comparison of a control preparation, and one from an alcoholic rabbit's brain, will show the following differences: The cell bodies and main processes in the normal are smoother and more even, the dendrites are broader, the gemmulæ are more even, thicker and feathery, they apparently spread out over more lateral surface, and are very regular in appearance; while in the alcoholic there is a gap here and there as if some of them had fallen off and disappeared. Indeed the differences between the two cells may shortly be expressed in that the whole appearance of the normal cell is stouter than its pathological fellow.

Among the cellular layers—and we take the pyramidal cells of all sizes as our chief exponent—we find a vast number of cells which show upon their protoplasmic processes one or more swellings of a rounded or elliptical form. Some of these tumefactions are very small and only to be noticed after close search, while others are so large as to immediately attract attention and excite suspicion that they are artifacts; and indeed it was only after a thorough examination by means of the electric light that we were enabled to disabuse ourselves of the idea that they were not artificial productions. Under the intense illumination of the electric lamp

they appeared as uniform reddish-brown bodies, divided longitudinally (under high magnification) by a series of fine lines converging upon the substance of the unthickened portion of the dendrite. The number of the swellings upon an implicated dendrite may vary very considerably; a dendron may be almost wholly filled with the swellings, at other times there may be only one or two of either large or small size (Figs. 3, 4, 7, 8, 9).

The process of tumefaction always appears to begin at or near the fine free extremity of the dendron, be it the extremity of the main apical process or one of its collateral branches, and not infrequently the extreme termination of the dendron is seen to be somewhat swollen when no other portion of the cell is involved.

Looking over the preparations a little closer we find numerous cells with moniliform swellings along the finer apical processes (Figs. 4, 6, 8, 9, 10), until a number are seen with the whole of the apical processes thickly studded with the bead-like swellings. Somewhat remarkable to relate, the basal dendrons are only exceptionally involved in the tumefactive process, though they do not escape alteration when the cell begins eventually to shrink in volume (Figs. 10, 12).

An essential accompaniment of the tumefaction of the protoplasm of the dendrons is the loss of the gemmulæ. The smallest swelling causes along its edges an evident decrease in the number of the lateral buds (Figs. 4, 6, 7). After the swelling has advanced to a considerable extent they all disappear, while in the intermediate stages all steps toward decrease and disappearance may be found. Between the points of swelling they are retained, but are often seen to be thinner and situated at more irregular intervals than normally. When long thickenings occur in the dendritic stems the buds are universally lost. The last of all the gemmulæ to disappear are the thicker branched ones that project at intervals some little distance beyond the others; and at times, though very rarely, they may still be seen clinging to the sides of some not far advanced swelling.

An accurate comparison, so far as outward appearances go, may be made between the moniliform swellings of the dendritic stems of the nerve cells and the swellings produced on the branches of some species of the oak-tree by a parasitic disease. Both have

the same knots and thickenings in their branches, even to the falling off of the finer lateral twigs of the tree when the disease has advanced to a considerable extent, and both may go on to produce a shrinkage of the substance, finally ending equally in decay and death of the cell and plant.

As the arterial changes found were comparatively unimportant in their character, it would be difficult to ascribe this widely extended and curious process of tumefaction of the dendrites and disappearance of the gemmulæ to nutritive changes solely from a defective supply of nourishment to the nerve cell, though truly the definite enlargement of the perivascular spaces would indicate that there had been some previous disturbance in the circulation of the lymph currents of the cortex. It would seem much more plausible to attribute the lesions to the direct action of the poison upon the protoplasm, though why it should take this peculiar form is difficult to determine. The alterations can hardly be of fatty nature, as the bodies of the unstained cells show nothing approaching a blackened condition from the action of osmic acid, nor anything unusual beyond the ordinary amount of yellow pigment granules, which in the rabbit is minimal.

It would appear from our specimens that the moniliform swellings of the dendrites and the loss of the lateral buds were the first steps in a pathological process which eventually was to end in the partial or complete disintegration of the cell structures, and with them the annihilation of the nervous forces produced by the cell, the latter, probably, preceding anything like cellular death; for clinically we see almost complete dementia alcoholica, when, according to the ordinary methods of staining, but comparatively few of the nerve cells show characteristic signs of degeneration.

Only a few of the nerve structures of the rabbit's brain give any evidences of deterioration of the substance of the corpus beyond those already described, though occasionally a neuron may be found which exhibits a more advanced degree of degeneration. Then the processes immediately adjacent to the body are roughened and seamed like the coarse bark of a tree; the staining of the altered protoplasmic substance is not perfect, the cell body is irregularly shrunken, the basal dendrites no longer stretch over

wide areas like their normal fellows, but have dwindled; the gemmulæ are lost, and the processes themselves are not stained for any distance from the corpus of the cell, but soon end in needle-like points (Fig. 11). Some of these cells might even be described as being corrugated, from the very roughened appearance of their exterior.

The nuclei of the nerve cells are seldom to be seen in silver preparations; occasionally a vacuole, occupying the spot where the nucleus usually lies, can be determined, and in its centre a black dot, probably the nucleolus, may be found if a careful search be made for it, but no details of the intimate structure can be determined. A few of the sections show curious defects in the impregnation of the cellular bodies, which can be equally seen in the control preparations. The dendrons and axons of the neuron are nearly perfect, while the cell body looks as if a portion of its substance had been scooped out down to the region of the nucleus. Such cell is depicted in Fig. 10. The process of unequal staining is undoubtedly what Andriezen has described as "channels and holes of liquefaction." All degrees of the apparent erosion may be present in different cells, from a single seam to excavation of more than one-half of the cellular protoplasmic substance. It is difficult to account for this defect in the impregnations, and it is one that is extremely liable to lead an observer into error. A cell may shrink perceptibly in volume and become roughened at the edges, but never in any of our sections have we met with any very considerable destruction of the corpus of the cell.

The axis cylinders of all the cells of the cortex were made the object of careful study, but no morbid alteration could be made out in them. This continuance of the axon, when other portions of the cell structures are far degenerated, is one of the peculiar features of the neuron which has before attracted attention, especially by Golgi (loc. cit.), who found that the axon resists to a greater extent degenerative processes than the dendrons, and may be found intact when the cell is reduced to a mere stump. In all of our preparations very numerous axis-cylinders were stained, and could be traced from their commencement at or near the basal end of the cell downward into the white layers, or upward toward the uppermost layer of tangential fibres; but no trace of unusual

varicosity or break in their continuity could be discovered. The collaterals ofttimes could be followed considerable distances, occasionally to their free endings, but nothing abnormal could be seen. Cells in an advanced stage of degeneration had as perfect neuraxons as normal ones, and could be traced equally long distances.

The Cortex of the Cerebellum.

The Golgi cells and the *Korbzellen* of Kölliker stained only in inconsiderable numbers, and but a few of those impregnated showed changes comparable to the cerebral cells. The Purkinje bodies, on the other hand, were luxuriantly tinged, sometimes an entire row being blackened by the silver and exquisitely brought out. A better comparison could therefore be made in these preparations between the number of degenerated and undegenerated cells, the proportion now being, when an entire row was taken, one degenerated to three normal ones.

Practically the same alterations were found with the Purkinje as with the pyramidal cells, though the changes were more prominent from their intensity. The loss of the lateral buds, from their greater luxuriance, was extremely striking; they disappear from the dendritic branches as an entirety, and on a considerably degenerated nerve body not a single one can be found (Figs. 15, 16, 17).

The stems of the dendrites also undergo atrophy, and in great measure disappear, only thick stems are seen arising from the corpus of the cell, which give off a number of short stumpy branches thickly studded with knotty projections in the place of the long feathery dendrites and their terminal twigs (Fig. 14). These twisted and shortened stems have numerous swellings in the longitudinal direction of their protoplasm. Those that still retain something of the form of a dendrite have numerous irregular swellings in the stems of the finer branches, the gemmulæ are almost universally lost, and the whole appearance is as if the dendrites had become gnarled and knotted by the action of some parasitic insect (Fig. 15). The cells that are least implicated have the rounded and longitudinal swellings along their finer stems, and the buds along the margin are fewer in number than elsewhere.

The degeneration of the Purkinje cells, while having the same general character as in the cerebrum, is much more striking, and there is no possibility of mistaking the process for anything else than it actually is—a parenchymatous degeneration of the cellular structures. Neither in the cerebrum or cerebellum is there any pronounced change in the support elements. The Deiters cells stain in neither region with any frequency, while the large-bodied vascular cells do not seem to have taken on any marked action, clinging to and surrounding the vessels after the usual manner, though they may possibly be a little swollen.

* * *

Before concluding this paper let us glance for a moment at the clinical picture of chronic alcoholism in order to see in what manner the pathological lesions and the symptoms correspond with one another. The epiphenomena of chronic alcoholism are so numerous that it will be difficult to do more than sketch the prominent symptoms: First come the sensory disorders, the exaggeration of the sensibility of the skin, the anæsthetic troubles, the ocular and auditory disorders; then follow the tremor, the tremulous articulation, the loss of tone in the muscular system, the tottering gait, the occasional paretic attacks, the inco-ordination, and, lastly, the intellectual disorders, the loss of moral force, the weakening of the mental faculties, the falsification of the judgment, the slowness of memory, finally the dementia, which is seldom complete.

The first of the three periods would correspond to the beginning of the vascular disorders, when the nerve cells, irritated by an insufficient supply of proper nutriment and excited by the presence of a poisonous stimulus, overact for the time, and then as nutriment is still withheld from them, altered metabolism results. The beginning swelling of the dendrites of the sensori-motor region is marked by paresthetic and anesthetic symptoms, those of the purer sensory region by visual and ocular troubles, and some amnesia, especially for recent events; or in other words, cells that have the function of evolving and transmitting thought cannot work properly, and defective memory results. Later, as the motor cells are more and more involved and nuclear changes begin, continuous tremor becomes apparent, the muscles no longer co-ordinate perfectly, unless for a moment under the direct influence of the will.

Still later, when a portion of the cell structures have become highly degenerated and the altered cells have become more numerous, the already tottering will-power becomes more and more deadened, memory and judgment fail, and when the degenerative process is far advanced, an incomplete dementia is the final result.

In conclusion, we do not consider the fact that only a portion of the cells of the cerebrum are involved in the degenerative process militates aught against the entire conception of the pathological entity. The nerve elements of the brain are intricately united one with another by means of their axons and collaterals, and are not able to function perfectly unless the normal relations to one another are preserved. A lesion in one cell will induce disorders in the function of two or more cells not involved by any morbid change, the intricate system of collaterals issuing from one cell influencing directly the impressions and nervous impulses arising from many others, and in this way a wide-spread disordered action of large numbers of the cerebral cells may be the result of disease in a comparatively few elements.

In the human being we have found the same degenerative process present as in the rabbit, varying only in degree, in some more intense, in others less so; but as the pathological lesions in chronic alcoholism in the human subject will form the basis of a subsequent paper, it will suffice here to say that they are practically identical with those in the rabbit.

We do not for an instant consider these lesions of the neuron described as peculiar to the effect of alcohol, but regard them as capable of being reproduced by any irritant drug or bacterial toxic product circulating in the blood, and acting for a considerable time on the living protoplasm of the nerve cell.

One point is made definite by this study—the fact that the alcohol, considered to be the least deleterious of all its series, exerts a very definite and destructive effect upon the nerve cell.

Explanation of the Photographs and Drawings.

PHOTOS.

Fig. 1. Nuclei of normal pyramidal cells of the rabbit's cortex, showing the nucleoli smooth and well defined. × 1100.

Fig. 2. Nuclei of the pyramidal cells of the alcoholic rabbit's cortex, showing the nucleoli roughened and enlarged. The outline of the nucleus is also more irregular than in the normal cell. Rabbit No. 10. ×1100.

Fig. 3. Beginning moniliform swelling of the apical process of a small pyramidal cell. Rabbit No. 42. ×265.

Fig. 4. Moniliform swellings in detached portions of apical dendrites. Rabbit No. 42. ×265. Micro-photographs by Dr. A. G. Hoen.

DRAWINGS.

Fig. 5. Small pyramidal nerve cell from the outer portion of the second layer, with normal body and basal dendrites, but with one branch from the apical dendrite showing moniliform swellings. The gemmulæ have disappeared wherever the swelling has begun. ×560.

Fig. 6. Small irregular nerve cell from the outer portion of the second cell layer, with advanced moniliform swellings of the principal dendrites and roughening of the cell corpus.

Figs. 7, 8. Advanced moniliform tumefaction of apical dendrites.

Fig. 9. An irregular pyramidal cell from the deeper portion of the second layer in an advanced stage of degeneration.

Fig. 10. Pyramidal cell from the deeper portion of the second layer with slight roughening of the apical process and normal dendrites. The corpus of the cell is excavated from its basal edge to the further limit of the nucleus.

Fig. 11. A medium-sized pyramidal cell, showing disappearance of the long dendrites and great roughening of the thicker stems, as well as complete loss of the gemmulæ. The cell body has a very irregular contour and is shrunken. The axon is intact. From a human preparation.

Fig. 12. Terminal portion of a dendrite of a Purkinje cell, showing the normal arrangement of the gemmulæ. From a control preparation.

Fig. 13. Portion of a process of a Purkinje cell from near the corpus. The longer branches and gemmulæ have entirely disappeared, leaving an irregular knotted stump.

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Figs. 14, 15, 16. Terminal branches of the dendrites of a Purkinje cell, showing the irregular swellings of the stems, loss of the gemmulæ, as well as the finer branches. Rabbits Nos. 6 and 41. All figures drawn with enlargement, Zeiss ocular 4, objective DD.

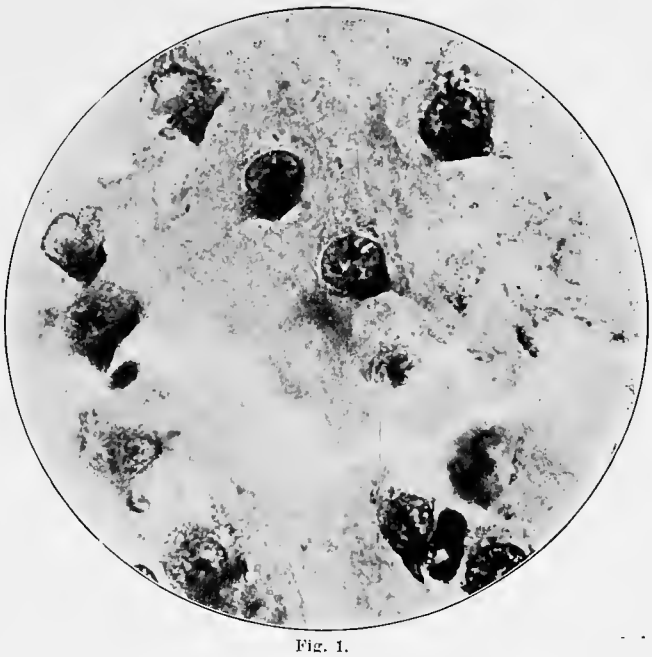

Fig. 1.

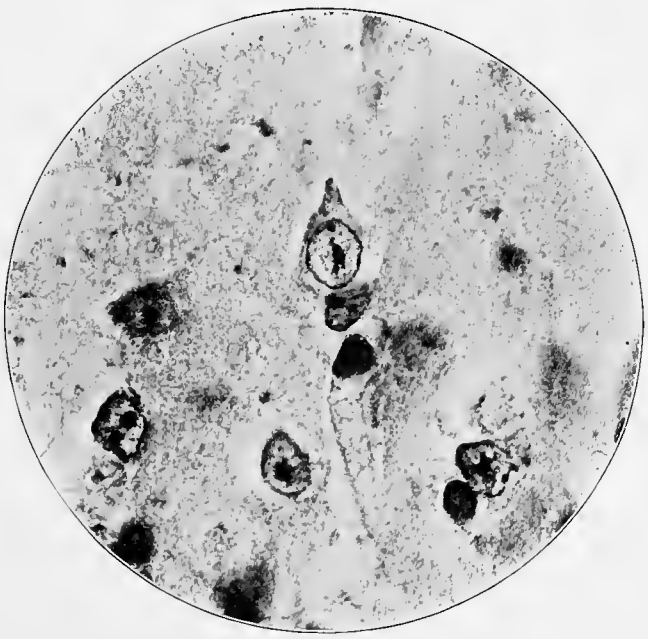

Fig. 2.

CHRONIC ALCOHOL.

PHOTO. BY DR. A. G. HOEN.

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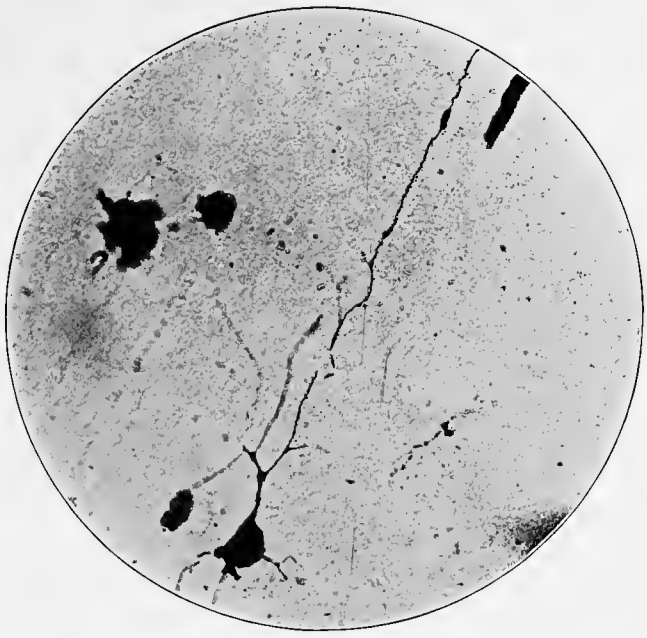

Fig. 3.

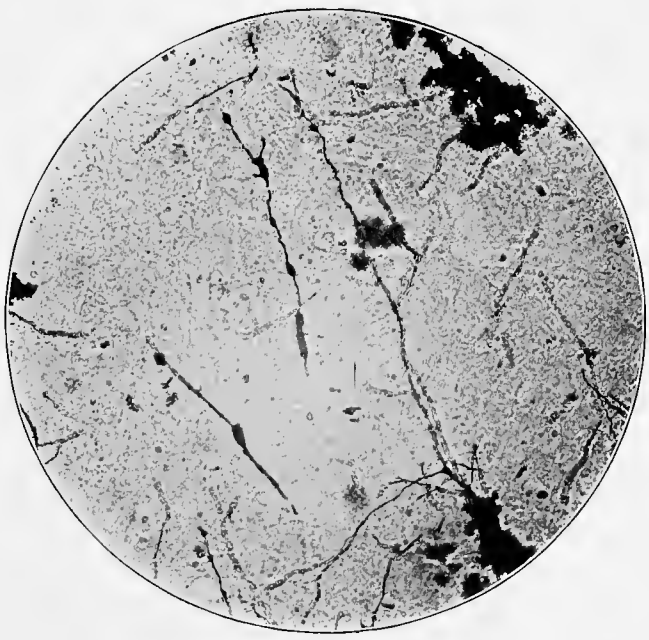

Fig. 4.

CHRONIC ALCOHOL.

PHOTO. BY DR. A. G. HOEN.

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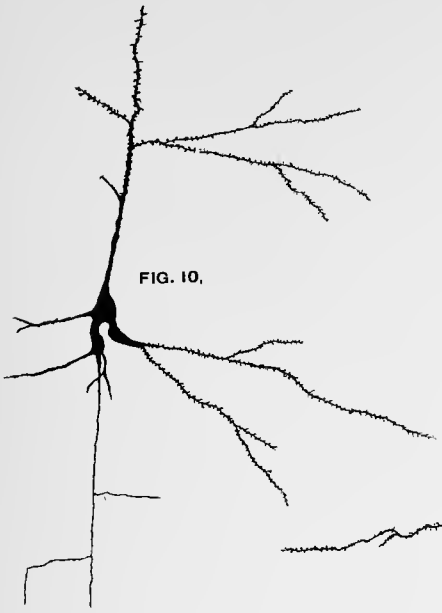

FIG. 10.

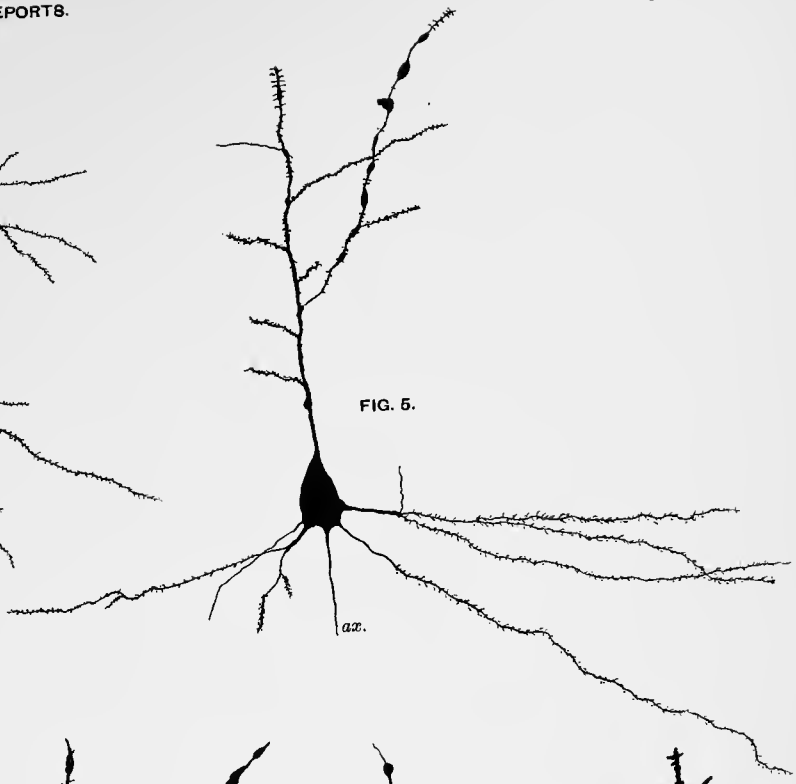

FIG. 5.

FIG. 6.

FIG. 7.

FIG. 9.

FIG. 8.

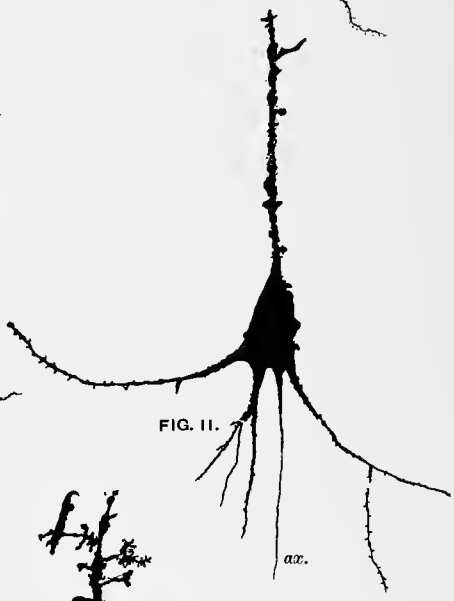

FIG. 11.

FIG. 12.

FIG. 13.

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CHRONIC ALCOHOL.

Section II.—Lesions of the Cortical Tissues induced by Acute Experimental Alcoholic Poisoning.*

The only literature I have been able to find on the subject of experimental lesions in acute alcoholic poisoning is contained in the incomplete article by Dehio (Centralblatt f. Nervenheilkunde u. Psychiatrie, March, 1895). He rapidly poisoned guinea-pigs with considerable doses of the drug, the largest amount reaching 25 cc. of 96% alcohol. Death followed in the most acute case in one hour, in the slowest in thirty-four hours. The method of preparing the microscopic sections was by the Nissl formula. The author confines his research on the cellular changes entirely to the Purkinje cells, and does not consider the vessels or their contents.

In the cases that died from the poisoning within a very short time no pathological lesions were found, but in those of longer duration he discovers changes in the chromatin structures of the cell, and greater receptivity of the protoplasm to the stain than is usual, but the nucleus and nucleolus remain unchanged.

These very slight lesions of the nerve cell are debatable on the ground that it is impossible with Nissl's method to constantly produce the same degree of staining, also that a definite alteration in the nucleus of a cell is of more positive value than greater or smaller absorption of a dye by the cellular protoplasm. In view of the results obtained from the present research, it is unfortunate that Dehio failed to note whether there were lesions of the blood-vessels' sheaths, or of their contents; for, as we already are aware, the soluble poison, ricin, is capable of producing decided degenerations of the elements of the vascular walls in much shorter time than thirty-four hours.

The three rabbits, whose brains were sent me by Dr. Friedenwald for the purposes of this study, were poisoned by a somewhat different procedure than in the foregoing work, namely, by slowly increasing doses of the poison until the animal had established a certain tolerance, and then increasing it to a considerable amount, which was maintained until the animal died, a method of treatment that does not differ widely from the course pursued by a man on a continued spree. While the doses are large they can hardly

*Plates VI and VII.

be said to exceed the amount taken by many men while on a debauch, and from which they eventually may recover, perhaps after an attack of delirium tremens or some other form of alcoholic psychosis. Thus a man weighing 150 pounds would take in the same proportion fifty times the amount of alcohol as a three-pound rabbit, and accordingly would obtain a daily allowance of 750 cc. absolute alcohol, equal to about 1500 cc. ordinary whiskey, with the difference that the ethyl alcohol is perhaps the less deleterious to the tissues.

I insert here a condensed table of the rabbit histories which shows some interesting facts. The loss of weight in the three animals is enormous. The first case lost approximately three-fifths of its weight, the second seven-twelfths, the third five-ninths, an enormous diminution, considering that the animals were fed and taken care of in the best possible manner, without which they could not live. Another point of note is that the resistance of the animals to the poison is not entirely proportionate to their weight, for the heaviest one received only a total of 165 cc. of alcohol, and the next heaviest, weighing thirty grammes less, received no less than 260 cc., nearly one hundred cubic centimetres more before the exitus.

Death occurred in all the cases approximately in three weeks. The principal gross anatomical lesion found at the autopsy was a fatty condition of the heart muscle, and this seems to be present in all animals subjected to continued administration of alcohol in which sufficient time between the doses is not allowed for complete elimination.

The Microscopic Examination of the Nervous Elements and Neuroglia.

The tissues of the brains were hardened in Müller's fluid and absolute alcohol. The staining was accomplished by the Nissl and silver phospho-molybdate methods.

With the aniline stain alterations are not very definite, beyond a few cells located in the immediate neighborhood of clogged vessels. Here the cellular protoplasm refuses, under the method, to show its stichochromic structure, appears uniformly and finely granular, and besides does not take up as much of the dye as

TABLE OF CONDENSED RABBIT HISTORIES.—ACUTE ALCOHOL SERIES.

No. in Series.	Age.	Weight at beginning of experiment.	Began to feed, 1895.	Quantity fed daily.	Died.	Weight at death.	Cause of death.	Gross anatomical lesions.	Total amount of alcohol fed in three weeks.
E.	Adult.	1220 gram.	Sept. 27.	5 to 15 cc.	Oct. 21, '95.	780 gr.	Rapid emaciation. Convulsions.	Fatty heart.	190 cc.
F.	"	1500 gram.	Sept. 30.	"	"	840 gr.	Rapid emaciation.	"	165 cc.
G.	"	1490 gram.	Oct. 2.	"	Oct. 24, '95.	920 gr.	Convulsions.	"	260 cc.

other more normal cells. In these individual nerve bodies there is beginning swelling of the nucleoli, which now fill out more than natural of the nuclear ring, and appear slightly roughened. The nuclear dust has not aggregated into clumps and become adherent to the nucleolus, as in some of the more chronic cases in the first study.

In the wide areas, where the disturbance of the circulation has been less well defined, changes in the protoplasm and nuclei of the cells are not very positive, and show almost entirely, in that the stichochrome particles of the protoplasm are seen somewhat less clearly than normal, and the protoplasm as an entirety shows greater receptivity to the aniline stain than is customarily seen in control slides, or better, will not bleach out with the same facility that it ordinarily does. Nucleus and nucleolus now appear to be strictly natural. The striated arrangement of the thicker dendrites of the neuron, near the cell body, is always seen.

The silver phospho-molybdate method shows much more positive changes than the Nissl, but these are confined entirely to the dendritic stems beyond the point where they become tinged by the aniline stain. These alterations in the dendrons are not seen everywhere in the section, but at comparatively frequent intervals, corresponding probably to the areas of greatest damage to the circulatory apparatus, for it should be remembered that the smaller vessels are no longer distinctly seen in the silver slides.

The departures from the normal in the dendrons have two forms: swelling of the branches and apparent atrophy. Dendrons in clusters in all layers of the cortex are seen to have irregular tumefactions in the course of their stems, extending over considerable distances in their long diameter, which suddenly decrease to the natural calibre of the stem. The majority of the gemmulæ are lost over the extent of these tumefactions, though here and there the buds are found projecting from the sides of the enlargement. Even the branches that have little of the tumefaction have considerable diminution of the lateral buds. The gemmulæ still retained have lost some of their chief characteristics; the rounded knobs of their terminations are lost, and they show only as even projections from the sides of the protoplasm of the stem of the dendrite. Often they have a larger than usual size from insertion

to termination, which would seem to indicate that they, as a portion of the protoplasm of the dendron, are swollen.

Quite as frequent as tumefaction of the dendrites is a process of apparent atrophy, with almost complete stripping off of the gemmules from the stems. This diminution of the calibre of the dendrites may be only apparent and caused solely by the shedding of the side projections, thereby producing an apparent reduction of the calibre of the stem, but varicosities are entirely absent from the dendrites of these neurons.

As far as can be determined, the axons and collaterals are not implicated in the process of degeneration, also no involvement of the cellular body can be found. Some of the corpora, it is true, stained incompletely, but whether this is owing to an imperfect impregnation with the silver salt or to damage to the protoplasm from the poison and defective circulation could not be positively determined.

The dendrons of the Purkinje cells seem to have escaped to a large extent the changes so apparent in the cortex of the cerebrum. Whether this is due to the difference in the circulation of the several regions I am unable to say.

Neuroglia.

The number of fixed tissue nuclei stained in the Nissl preparations does not indicate an increase in the numbers of these elements throughout the cortex. In the silver slides the support elements proper, so far as the stain shows, present no variations from the control, but on the other hand the vascular neuroglia gives indication that alterations are taking place within its structures, and show considerable variations from control preparations. The cell bodies are larger, the protoplasmic extensions are thick and knotty, and the arms extending toward neighboring vessels are more prominent than in the normal. Altogether, the impression is given that these cells are somewhat swollen.

Changes in the Blood-vessels seen with Nuclear Stains.

Arteries and Intermediary Vessels.—The nuclei of the endothelial cells are everywhere swollen, and in places are fragmented and receive either too little or, more rarely, too much of the dye.

The cell substance is also distinctly undergoing retrogressive alterations. The cells of the intermediary vessels look as if they had been subjected to severe strain, as their even contours are distorted and have many irregular bulges in their outlines.

The changes in the muscularis of the arteries are equally interesting. Nuclei are now and then absent from areas of the median wall of the vessel, and in those that remain certain abnormalities are apparent; one-half of a nucleus being occasionally unstained, presenting the appearance of a vacuole, while in the other portion the chromatin particles take the stain fairly well, and the karyoplasm also receives a portion of the dye. The nuclear membrane surrounding the entire nucleus is distinct and stained. But it is in the substance of the muscular protoplasm that the lesions are most apparent, and show that the cells are undergoing a retrogressive process. They no longer have their substance clearly stained, but it is turbid, even hyaline in appearance. The protoplasm too is considerably swollen, and its receptive quality to the dye is no longer good. The Virchow-Robin lymph space is entirely obliterated, and in those portions where the tumefaction is most pronounced there is also almost complete obliteration of the His lymph space, the outer lamina of the vessel being pressed closely against the limiting membrane of the perivascular sheath.

Changes in the adventitia are not so distinct as in the two inner coats, though in places it holds considerable numbers of leucocytes, or they may be lying packed between it and the outer wall of the lymph space. These elements are swollen and necrotic.

The contents of the perivascular spaces, where the degree of compression is insufficient to obliterate them, are instructive. There are large numbers of leucocytes in various stages of degeneration, and, besides, there is frequently a number of large protoplasmic bodies, several times the size of a polynuclear leucocyte, very granular and without nucleus, that probably are formed from the remains of partially broken-up lymphoid corpuscles that have aggregated into crescentic or oval forms. Besides these bodies there is a quantity of detritus, finely granular in character, not sufficient to cause without the aid of the lymphoid cells any blocking of the nutrient currents. Osmic acid produces a slight blackening of the degenerating white corpuscles, also of the detritus within the spaces.

The capillaries, like the intermediary vessels, are tortuous and twisted, their nuclei show changes similar to those in the larger vessels, and the cells have departures from the normal in staining, and here and there in the lumen are plugs of white blood corpuscles, which, from their closely packed appearance, must have entirely stopped the circulation of the blood in the vessels before death. The lumen beyond the plugs is entirely empty of any contents.

Veins.—Changes in the coats of these vessels are similar to those in the arterial system, but aggregations of dying polynuclear corpuscles are more frequent, and are by far the most striking feature both of their contents and surroundings.

These aggregations, which may vary from three or four to a dozen or more, are located both within and without the lumen of the vessel (especially the smaller ones). Within the lumen are collections of white blood corpuscles filling the interior, and numbers are seen penetrating the walls. So vast are the collections in the perivenous spaces that the whole cavity is occasionally filled, and backward pressure from the plugs and compression of the vessel from the outside have attained such a height that in a number of instances the vessel's walls have ruptured and red corpuscles are intermingled with the white and fill the space completely. In one instance the site of the rupture was located in the section. All the leucocytes within and without the vessels show more or less evidences of degeneration, in some extending to erosion and disintegration of the cells.

The individual arteries, particularly the medium-sized ones, are quite differently affected by the morbid process, some showing lesions of a character much more advanced than others. This would appear to depend largely upon the numbers of lymphoidal plugs, both in the smallest arteries and capillaries; for where they are thickly scattered, there the amount of arterial degeneration is greatest, particularly the lesions of the important muscularis. It would thus appear that at some period antedating the death of the animals, collections of leucocytes formed in the smaller vessels and veins, and a slowly increasing backward pressure began upon the arteries, not sufficient, it is true, to occasion complete stasis, but enough to create unusual pressure upon them, and this

pressure, in combination with the poisonous effects of the alcohol carried with the nutrient fluids, caused degeneration of the cellular elements forming the blood-vessels' walls; the stress of the action falling upon the inner coats of the arteries.

This severely increased pressure is probably only an exaggeration of what ordinarily follows the administration of a moderate amount of alcohol to an animal. There soon follows the ingestion a dilatation of all the arteries of the body from the paralyzing action of the drug on the vaso-constrictor nerves, and this endures a variable time, according to the quantity of alcohol taken. But the apparent fact that the gray substance of the cerebrum has a different innervation for its arteries from other portions of the body becomes in this instance a factor of great importance. Vascular nerves may be found without trouble or difficulty in muscles, glands, etc., by the silver and other stains, but in the substance of the encephalon they are never to be seen with similar staining methods; hence it is fairly reasonable to suppose that they are not present in this location and that some other controlling mechanism takes their place. I have most carefully looked for them in many brains, both human and of the lower animals, but have never seen the slightest trace of their presence within the nervous structures. They are to be readily found in the soft meninges of the brain and in the choroid plexuses, but nowhere within the proper substance of the cerebrum. Tuke and Andriezen, who have made researches in the same field, have also failed to find them.

The mechanism controlling the cortical arteries is therefore presumably different from that in other portions of the body, and the muscular cells are less directly under the influence of nerve control. What is the result when we have a stimulant administered? The muscular cells, under the influence of the direct action of the poison, and free from any power to urge them to contract after the immediate effect of the toxic substance is passed, remain for a long time inert, the congestion of the cerebral tissues is long continued, larger amounts of poisoned blood pass through the brain, and incidentally a greater proportion of alcohol than to other tissues; the deteriorated serum is transuded in increased quantities, it is carried into the lymph spaces surrounding the cerebral cells,

their structures are bathed in the diluted alcohol, and their activity is dulled by the narcotic, weakened as it is by the serous fluid; inertia and torpor of the functional activities of the cells are the result, and it is only after the long continued elimination of the poison from the system that they resume their normal functions.

If the quantity of the poison to which the tissues are subjected is very considerable and continued from day to day, and the emunctories become clogged for a long time, the damage to the vascular wall is proportionally greater. Judging from the present cases, the damage may proceed to necrotic changes in the endothelial and muscular cells, leucocytes formed in other portions of the body accumulate in the cerebral vessels from the increased amount of blood brought by the arteries not being carried off promptly by the venous system, and therefore we have a constant accumulation of these corpuscular elements, terminating finally in blocking of the capillaries and smaller veins, diapedesis, choking up of the perivascular lymphatic channels, finally clogging of the lymph flow, and eventual damage both to the walls of the arteries by backward pressure acting on a tissue already prone to undergo degenerative changes from the deleterious effects of a poisonous drug, and to the veins from abundant extravasations and transudations of the corpuscular cells.

In conclusion, the large dependence of the lesions of the nerve elements upon the vascular is very readily demonstrated in the Nissl slides by all the alterations of importance being in the neighborhood of damaged vessels, while those supplied by a more steady current of nutrient fluid show only uncertain departures from the normal in their chromatin. It is hardly necessary to add that these latter lesions, though slight, are but the precursors of deeper degenerations of the protoplasm, which eventually show in the nuclear alterations of the more chronic cases. It would appear as an interpretation of the significance of the silver preparations that considerable destruction may take place in the dendritic stems from the combined effects of the alcohol and the damage to the nutrient supply, and that these lesions may be present in an advanced degree before any implication of the corpus with its inner structures is discoverable.

The lesions of the blood-vessels and their contents are pre-

eminently the most important facts established by this study. We have in some measure already advanced the theory that changes in the constituent elements of the blood are among the first alterations produced by the poisonous effects of alcohol on the blood-forming organs; in other words, alcohol has a decidedly disturbing influence on the blood formation. This is in conformity with what is seen in the clinic, and may at some future time form the basis of an interesting blood investigation. The exceeding abundance of the polynuclear leucocytes in and around the cerebral vessels of the rabbits shows that there is most probably excessive production of these elements, but we know nothing of the numbers of the red corpuscles, though in all likelihood there is the same diminution as in so many other anæmic states.

The formation of the many thrombotic plugs of lymphoidal elements is very remarkable and interesting, as are also the numerous transudations of these corpuscles through the vascular walls; indeed, so numerous were they in some instances that they compressed the sheaths of the small intermediary vessels and practically closed them.

The study has shown what has never before been demonstrated, that poisoning with alcohol in considerable doses, continued over a moderate time, will produce decided and ascertainable lesions of the nutrient structures and nervous elements of the cerebrum, very similar in character to the pathological lesions produced by other more virulent soluble poisons. One point should be borne in mind between this study and a similar one upon the human alcoholic brain, that man has through long generations been accustomed to the use or abuse of alcohol in some form, and has established a certain degree of tolerance to the drug, and therefore the poisonous effects will be less pronounced than in animals that have established no hereditary tolerance.

Descriptions of the Drawings and Photographs.

Drawings.

Fig. 1. Primordial dendrite of a pyramidal cell with advanced irregular tumefaction of the stem and branches. The loss of the lateral buds is very considerable.

Fig. 2. Pyramidal cell, showing thinning of the dendrites with diminution of the lateral buds. Zeiss, ocular 4, objective DD.

Photographs.

Fig. 3. Polynuclear leucocytes in the perivascular space of a small intermediary vessel compressing its walls. At one point the lumen of the vessel is seen to be obliterated. × 280.

Fig. 4. Leucocytes in the blood in a cross section of a large vein. × 280.

PART II.—SERUM POISONING.

Experimental Lesions induced by the Action of Dog's Serum on the Cortical Nerve Cell of the Rabbit's Brain.

The interest that has been recently taken in the action of a number of soluble bacterial poisons produced in the course of certain infections diseases capable of inducing various epiphenomena from their effect upon the central nervous system, is well attested by numerous articles from the pens of authors in the four principal languages of the civilized world. The endeavor of the majority of these workers has been to discover in the corpus of the nerve cell certain definite changes by means of selective stains, rather than to take up the several members of the neuron and consider them separately, and indeed this has only recently become possible.

While it is possibly stretching a point to consider blood serum in the light of a bacterial poison, its effect upon the tissues is not dissimilar, as may be seen by the results of the examination of other organs than the cerebrum from rabbits dying of chronic serum poisoning, and it is highly probable that we will eventually find in every person dying after the continued action of soluble poisons, whether bacterial or chemical, a similar class of lesions of the neuron as those described in the following pages.

In the pathological material from the autopsy table we are sadly hampered by a multitude of post-mortem and other changes, which, though of great moment, are imperfectly known; therefore experimental material, under full control from the moment the inoculation is made, through the various stages of the experiment, down to fixation, staining, and mounting of the sections, is of the utmost value in establishing a precedent for a similar class of nerve cell lesions in the human being, especially as there are no wide anatomical differences between the nerve cell of the animals used and man.

The material, for the purposes of this study, consisted of the cerebra of five full-grown rabbits that had been subjected for a

number of months to chronic poisoning from injections of blood serum into their bodies. The animals become stupid, emaciate, and finally die from exhaustion.

It is to my mind proved by the destructive influence of the poison on the nerve cells of the cortex, that it requires only the long-continued action of any soluble toxin to cause destructive effects on the neuron, and does not at all call for the presence of a micro-organism. This principle may be more clearly demonstrated in the succeeding article, and it will probably eventually be shown that poisons that are supposed to be limited in their action, are universal nerve poisons; and that their continued influence results in an extensive degradation of the entire nervous system, if only sufficient time be allowed for their operation.

During the winter of 1893, Dr. Flexner, of the Pathological Laboratory, began a series of experiments upon the action of blood serum obtained from man and the dog, upon the rabbit. These researches have been continued, though in 1894 he published (Med. News, Aug. 4) an outline of the pathological changes found after the inoculations in connection with a series of studies entitled "The Pathologic Changes caused by Certain so-called Toxalbumins."

Briefly, Flexner found that injections of serum of 1.5 per cent. of the bodily weight of the animal experimented upon were eventually fatal, death occurring either immediately or after the lapse of ten or twelve hours. Quantities of 1 per cent. of the bodily weight caused profound disturbances, including hemaglobinuria and albuminuria, less commonly anuria, and in a few instances immediate death. When the exitus followed immediately upon the inoculation, it was usual to find thrombi in the right side of the heart, which now and then extended into the pulmonary artery and its branches. Cases in which the death of the animal was delayed for a time were of especial interest, as they showed well-marked lesions, resembling in many ways the changes described in connection with the toxalbumins of diphtheria, ricin, and abrin.

The organs studied were the spleen, liver, kidney, and lymph glands. In the acute cases the spleen showed tolerably rich fragmentation of nuclei, situated especially in the Malpighian bodies; the liver, certain foci of cellular necrosis; while the renal epithelium was degenerated, and many casts blocked the kidney tubules.

In one animal dying on the thirteenth day very extensive lesions were found. The microscopic appearances were those of chronic interstitial processes in the liver and kidney. In the latter organ the tubules were in places atrophied and surrounded by a new growth of connective tissue, in other places the tubules were dilated and the epithelial lining degenerated. In the liver the chronic changes were exceedingly well marked, and were an accurate reproduction of cirrhosis in the human being. Areas of newly formed and forming connective tissue proceeded from the portal spaces and from the capsule; newly formed bile ducts are numerous, but what was of special moment was the association with these changes of another process; acute degenerative changes in the liver's substance, which were often distinctly the starting points of the sclerosis. In the spleen masses of fibrous tissue were found. These changes show that the damage the serum is capable of doing is not limited to the corpuscular elements of the blood, for the tissue cells are not indifferent to its action.

From a later series of experiments than those just referred to, Dr. Flexner very kindly placed at my disposal the cerebra of several of the rabbits, in order to enable me to determine if the cerebral cells suffered from the action of the serum poisoning in a manner equivalent to those of the viscera mentioned above.

Unfortunately for our closer knowledge of the cerebral cell, these elements do not show mitotic figures, nuclear fragmentation, and coagulation necroses in the manner of the liver cells, but to our best stains, whether chemical combinations with the cellular substance or simple dyes, are eminently stubborn to microscopic analyses; and from the reaction of the protoplasm to the dyes we can demonstrate in cells we perforce know must be diseased, only indefinite alterations in the amount of the absorption of the dye by the protoplasm, especially in the chromophile particles, and most uncommonly in the nucleus and nucleolus. These difficulties in obtaining accurate results from minor changes in the nerve cell probably arise from the circumstance that the nerve cells are in a measure completed elements, and are incapable of regeneration as other cells are, and only show alterations of a pronouncedly degenerative type.

The material for this study has been to the present time the

brains of five rabbits from parts of three series of serum experiments, and, so far as the lesions of the cortical cells were determined, they were constant and identical in all the animals, though varying in intensity, seemingly according to the severity of the poisoning, as rabbit No. 2, first series *a*, which died from the result of an injection, and not from the long-continued poisoning the others underwent, exhibited a vastly larger number of normal cells than its companions of the investigation. It will be noticed in the table that this rabbit lost only about two hundred grammes in weight during the experiment, and accordingly was not so greatly emaciated as the others. It is at present impossible to determine exactly what part the denutrition of the tissues plays in the production of the lesions of the nerve cells, but from the discoveries of Monti in this direction we can hardly doubt that it is very secondary to the direct influence of the poison upon the cell, and in human alcoholics that show no emaciation the same class of lesions is found, varying somewhat in intensity.

A synopsis of the histories of the rabbits comprising the basis of this study is given in the accompanying table.

The Methods of Preparation and Staining.

The methods pursued for the preparation of the cerebral tissues for this investigation were similar to those made use of in Part I of these studies, namely, fixing the tissues in alcohol and in Müller's fluid, and after treatment by various anilines, hematoxylin, and silver staining according to the silver phospho-molybdate formula, as already given. The control preparations were obtained from the brains of two young but full-grown rabbits, treated exactly by the same formula for the fixing and staining, kept for the same length of time in the hardening media and stained exactly by the same procedure as the serum brains, often running the two together in the same jars.

As mentioned in the first section of these studies, there are upon the dendrons of the nerve cells of the cortex a very minimal number of thickenings or varicosities. The majority of these occur at the forkings of the dendritic branches, and rarely indeed is one to be found in the course of any of the finer branches in the normal brain. In the continuance of the axis cylinder there are also

Chronic Serum Rabbit Series.

Number in series.	Age.	Weight at beginning of experiment.	Began to inoculate.	Quantity injected.	Frequency of inoculation.	Died.	Weight at death in grammes.	Clinical cause of death.	Gross anatomical lesions.	Remarks.
1. Series. 2, *b*.	Adult.	1700 gram.	Nov. 22, 1894.	6 cc. increased to 18 cc.	Intervals of two weeks.	Apl. 8, 1895.	1200	Toxæmia.	Great emaciation. No visible lesions.	There were no marked meningeal changes in any of the rabbits.
2. Series. 1, *a*.	"	1700 gram.	Nov. 6, 1894.	"	"	May 5, 1895.	1500	Overdose of serum.	Thrombi in heart and brain.	Injections of 12 cc. were fatal in control rabbits.
3. Series. 1, *b*.	"	1800 gram.	Nov. 6, 1894.	"	"	May 31, 1895.	1300	Toxæmia.	Cirrhosis of liver.	Rabbit 2 died suddenly after an injection of serum.
4. Series. V, *a*.	"	1470 gram.	Oct. 19, 1895.	6 cc. increased to 10 cc.	"	Dec. 3, 1895.	1470	"	Cirrhosis. Thrombi.	Several rabbits had convulsions at time of death.
5. Series. B, *a*.	"	1700 gram.	Nov. 23, 1895.	"	"	"	1640	Thrombi in heart. Toxæmia.	No gross lesions.	

knots of somewhat greater frequency, which begin at a variable interval from the cellular body, and continue through the entire intracortical course of the axon.

Occasional varicosities in the dendron must therefore be held to be normal, the same holding good for the axon, although they are present in the latter with greater frequency. Since Colella, Greppin, Andriezen, and a few others have found in human brains, principally those from paretic dements, an increased number of swellings upon the dendrons, the subject of these varicosities has attracted some little attention. Flatau (Arch. f. mik. Anat., May, 1895) has quite recently discussed them at some length and has arrived at the conclusion that they are natural.

It is quite possible to imagine that the neurons of normal brains have a varying number of varicosities upon their dendrons, but when they increase vastly in size and occupy the whole dendron they must be held to be abnormal, especially when they present a size that is incompatible with anything in the control preparations; and the entire cell, with the exception of the axon, frequently shows evident signs of the presence of a destructive process. Not only are these abnormal swellings of great frequency on the finer branches and along the large stems of the pyramidal nerve cells, but it may readily be demonstrated that the very varicosities normally present, particularly the enlargements at the branchings of the dendrons, take on this alterative process and in themselves become tumefied.

Furthermore, we have one certain sign of degeneration, in the pyramidal and some other of the nerve cells, that seems to have entirely escaped the attention, not only of the criticisers of the value of the degeneration, but also of its exponents. I refer to the disappearance of the gemmulæ or lateral buds upon the branches of the dendrites, which takes place whenever the tumefactive process is at all advanced, or even occurs coequally with it.

I have elsewhere written more fully of the gemmule and its histological significance, also in certain forms of dementia (Med. News, Nov. 9, 1895), and it now suffices to give a short anatomical description of one very interesting part of certain of the most important of the nerve cells, that for some unexplained reason, probably though from defective staining, has hitherto obtained

but little attention. The gemmule in its most developed state is found only on the dendrites of two classes of nerve cells: the psychical or pyramidal cells of the cerebral cortex, and the Purkinje cells of the cerebellar cortex. Histological differences in the appearance of the gemmulæ are very apparent between the two varieties. With the pyramidal cells they present very much the appearance of a thin pin with a rounded head, with its sharpened point stuck into the protoplasmic substance along the edge of the dendrons, both the ascending and basal of the cells. They are arranged with considerable regularity along the thicker protoplasmic branches, and at a rectangle with the stem of the dendrite. On the finer dendrites the interval between them is slightly increased, and while preserving the same form as on the thicker branches, they are slightly longer and have less of the rectangular disposition. On the branches of the Purkinje, the gemmulæ are very numerous and much more closely set together than on the pyramidal cells, and give to the neuron a furry appearance. Besides these inherent characteristics they begin by a broader base, do not increase in size as they extend outward, and terminate not in a rounded knob, but in a flattened ending which is no larger than the proximal portion of the stem. Here and there, between the others, single ones are seen, similar in appearance to those of the cortical cells.

The function of the gemmule is in all likelihood to receive nerve impulses from the endings of the numerous terminal nerve fibres that seem almost to touch them, and carry these impressions to the dendrite, and by its medium on to the cell body. Differences in the function of the gemmule of the pyramidal and Purkinje cell are probable.

Histology of the Alcohol-hardened Serum Preparations.

The staining of the sections for this portion of the study was by Nissl's methylene blue and magenta methods and by hematoxylin-eosin. The only noticeable difference between the several brains was that in Nos. 2 and 5 the perivascular spaces contained a considerable number of polynuclear leucocytes, while in the other specimens these corpuscular bodies were present only in small numbers.

The larger and medium-sized arteries have absolutely no sign of alteration in their several coats. The intermediary vessels are not at all prominent, their sheaths are normal, and the perivascular spaces, while distinct, are not enlarged and contain no foci of round cell aggregations or hematoidin debris. The capillaries and veins are normal. The endothelial lining of all the vessels has no distinct swelling of the nuclei.

The staining of the nerve elements by the Nissl methods was made as intense as possible, and the decoloration not allowed to proceed quite to the usual point in order to obtain the protoplasmic processes stained to their fullest extent.

The nuclei of the nerve cells do not seem to be shrunken or abnormal. Few of them are of other than the mononuclear variety. This nucleolus is smooth, lies toward the centre of the nuclear ring, and shows no alterations in its capabilities for the absorption of the aniline.

Changes in the protoplasm of the corpora of the cells are somewhat indefinite. The protoplasm takes the aniline stain well, but the chromophilic particles are not well defined, and the spaces intervening between them seem to be more filled with fine granules than in the control. No stress can be placed on these indefinite changes.

A very few of the pyramidal cells contain vacuoles, but not even as many as three in a section. Seldom is there any appreciable shrinkage in the protoplasmic body ascertainable. The protoplasmic arms of the cells are very finely granular. In some of them small knots are to be seen, the swelling being recognizable from the absorption of a greater quantity of the dye than the portion more distant from and more proximal to the cell body. In the swelling the fine granules become less distinct than elsewhere.

In the cerebellum there is nothing noticeable in the cells of the granular and molecular layers.

Pathological Histology of the Silver Phospho-Molybdate Sections.

Between brains Nos. 1, 3, 4, 5 there were no microscopical differences. Brain No. 2 showed a lighter degree of degenerative changes in the neurons than the others, and was especially interest-

ing from the fact that the degenerated could always be found intermingled with approximately normal cells, affording an opportunity for an accurate comparison between the different elements. This brain was also remarkable for the beautiful staining of the nerve elements of all the layers, which were exhibited in as perfect a manner as can ever be obtained in silver preparations, and the sections were not disfigured by the presence of precipitate, even the external margins being free.

The lesions found in all the cerebra were closely allied to those in the alcoholic brains that formed the material for the first study. Cells of all layers were involved in the destructive process, the pyramidal of all varieties in the first order, then the deeper-lying elements, finally those of the extreme outer edge of the second layer, and the elements of the molecular lamina.

A view of a section under low enlargement reveals that the primary processes of many of the pyramidal cells no longer reach into the outer portions of the molecular lamina; their finer dendritic branches have disappeared, while the thicker ones are filled with a multitude of coarser and finer knots, scattered with some regularity along the line of the stem. On the other hand the thick intracapsular portions of the dendrites have not become diseased in a similar manner, but apparently retain their integrity, in so far that they are not altered in appearance by coarse changes, and seldom does the body of the cell present aught but its even rounded contour. The basal processes are often likewise shortened, and show the knotty growths upon them like the ascending dendrons of the cells.

Not every nerve element presents a similar degree of alteration, and according to the amount of involvement they may be divided into three classes: cells in which the process is beginning; those in which it is moderately advanced; those which have the dendrons very much degenerated.

The normal cells in brains 1 and 3, also 4 and 5, were comparatively infrequent; in No. 2, on the contrary, more than two-thirds of the stained cells were normal.

As the degenerative process is of similar character among all the classes of cells, we have taken the most prominent type, the pyramidal, as the criterion of the whole, since they are very much

easier to study than the others, from their definite size and anatomical characteristics as well as constant staining.

Class a, Cells slightly involved in the Degeneration.—High up in the molecular layer we find upon the finest branches of the dendrons of the pyramidal cells, especially those of the long-apical process variety, a few tumefactions of either rounded or elongated form in the course of the stem. These swellings are deeply stained by the silver salt, are smooth, and have few or no gemmulæ attached to their sides, or when they are still present there are perceptible differences in the tingeing by the silver salt that indicate an alteration in their structure. Both nearer the cellular body and more distally from the swelling the dendrite appears to be perfectly normal, the staining is good, and the pin-like lateral buds are numerous. In these neurons the coarser branches and the corpus of the cell are undisturbed by any alteration apparent to the microscope, and indeed the slight swellings of the finest twigs would occasion but slight comment were no other cells more deeply involved.

Class b, Cells moderately involved by the Degeneration.—This type is the most numerous of all. The tumefactions before present only on the finest dendritic branches now extend through the entire path of the stems of the apical and basal processes, reaching up or down to their intracapsular portion, and many of the finest branches are no longer stained, and are apparently totally degenerated, having been partially or totally removed. The number of the swellings varies greatly in the different involved cells. Usually the dendrons have a large number of small thickenings along their course and present a true moniliform appearance. Less commonly there are only a few of larger size, but the result to the nerve process is the same. These large-sized swellings are peculiarly frequent at the forkings of the branches of the apical dendrites, where there is normally a thickening of the protoplasm. Rarely one meets with dendrons in which the smaller swellings are so numerous that they are coalesced, and only are noticeably different from the normal dendron by the irregularity in their contour and loss of the lateral buds. In all the varieties there is an absolute loss of the gemmulæ on the dendritic process, which eventually proceeds to a complete stripping off the dendron of all its finest rectangular pin-like processes.

of this portion of the neuron. Cells that are somewhat eroded and roughened in their bodies have perfect neuraxons, and these may be traced far downward into the white medullary layers. Cells which are apparently almost totally destroyed are too few to allow of any accurate examination of their axons. The collaterals from the axis cylinders of the pyramidal cells can be followed to their bulbous free extremities, nor do the fibres, coming from more distant regions and passing upward to terminate in the molecular lamina, show anything but a perfectly natural condition. There is no increase in varicosity, no breaks in the staining of the nerve thread, no difference in the appearance of the terminal apparatus.

Cortex of the Cerebellum.

The changes in the nerve bodies resemble those in the cerebrum, but are less intense. The twigs of the Purkinje cells are often bared of their protoplasmic fur, have an occasional swelling, but are not highly degenerate. Normal Purkinje cells preponderate over abnormal ones. The finer free extremities of the dendrons show the alterations to a greater extent than the ones closer to the corpus of the cell, as if the swellings were just beginning. The neuraxons of these bodies are distinct and perfect. The *Korbzellen* stain infrequently, and nothing definite can be said of them. The Golgi cells are well shown, but alterations in them are slight.

Very numerous axons from the *Korbzellen*, Golgi, and recurrent branches of the Purkinje cells are well stained in the molecular layer, but show nothing abnormal. Some beautiful specimens of the arborescent endings of the fibres intermingling and terminating among the branches of the Purkinje cells were found, but they were perfectly normal, to all indications.

The neuroglia structures, both in the cerebrum and cerebellum, in Cases IV and V, were better tinged than in the other brains. The long and short rayed cells show no structural departures in their protoplasm from the normal preparations. The peculiar support cells along the pial margin are closely set together, but their feathery filaments are not thickened. On the other hand the bodies of the vascular neuroglia are greatly swollen, globular in

outline, and in this enlargement their various processes participate and show as large thickenings of irregular outline. This enlarged condition of the prolongations is even more apparent in the arms that extend to the neighboring vascular sheath, along with their terminal knobs. Thick groups of these swollen cells surround nearly all the vessels of any size in the gray layers. The degeneration of the nerve cells is therefore a simple non-inflammatory process, unaccompanied by any proliferation of the support elements, and the vascular neuroglia cells participate only in the alterations by reason of their connection with the lymphatic absorbent apparatus.

While the small number of the pathological serum brains does not allow us to speak with entire positiveness of the lesions of the cortical cells, yet from their constancy in all our preparations it is more than probable that they belong to a new class of degenerative changes of the nerve cell that will ultimately prove of the greatest importance in a long series of irritative abnormal conditions in the human subject, and will also open up a new field for the student of mental changes.

The absence of vascular lesions of importance precludes the possibility that alterations of nutrition from disease of the vessels are of the first importance in the production of the degeneration of the dendron. Much rather would we refer them to the direct action of the toxalbumen upon the cellular protoplasm, causing, in some unknown manner, at first swelling of the substance of the dendron, and later atrophy and destruction.

Drawings and Photographs.

Fig. 1. Pyramidal cell from the mid-portion of the second cellular layer of the rabbit's brain, showing commencing tumefactions of the protoplasm of the finest apical dendrites, and denudation of the gemmules at the points of swelling. At the uppermost forkings of the ascending dendron a normal enlargement of the protoplasm is seen, which is covered by gemmules. Ax., Axon.

Fig. 2. A cell of different form from the same region of the cortex, showing an increased number of swellings and greater loss of the gemmulæ. Ax., Axon.

Fig. 3. A cell from the same region showing atrophy and

destruction of all the dendrons. The gemmules are only present at one point on the ascending process and the cell body is considerably eroded.

Fig. 4. Small pyramidal cell, showing complete loss of the protoplasmic branches and gemmules, with roughening and shrinkage of the cellular body.

Fig. 5. A long-apical process pyramidal cell from the lowermost region of the second cellular layer, showing the swellings and shortening of the ascending process, and greater disintegration of the cell body. Zeiss, ocular 4, objective E.

Fig. 6. Micro-photograph of a stout ascending process of a large *normal* pyramidal cell, showing the arrangement of the lateral buds. A number of finer dendrons are included in the photograph. The fine granular lines indicate dendrons and vessels not fully in the focus of the camera.

Fig. 7. Micro-photograph of the finer portion of the ascending process of a normal long-stemmed pyramidal cell, showing the arrangement of the gemmules.

Fig. 8. Micro-photograph of the ascending process of a pyramidal cell from a serum brain at the same level as Fig. 7. The tumefactions and loss of the gemmulæ are very distinctly shown.

Fig. 9. Micro-photograph of the bifurcation of the long process of a pyramidal cell from a serum brain, showing a swelling of the normal enlargement at the forking, and large knots in the course of the finer branches. Enlargement about 550 diameters.

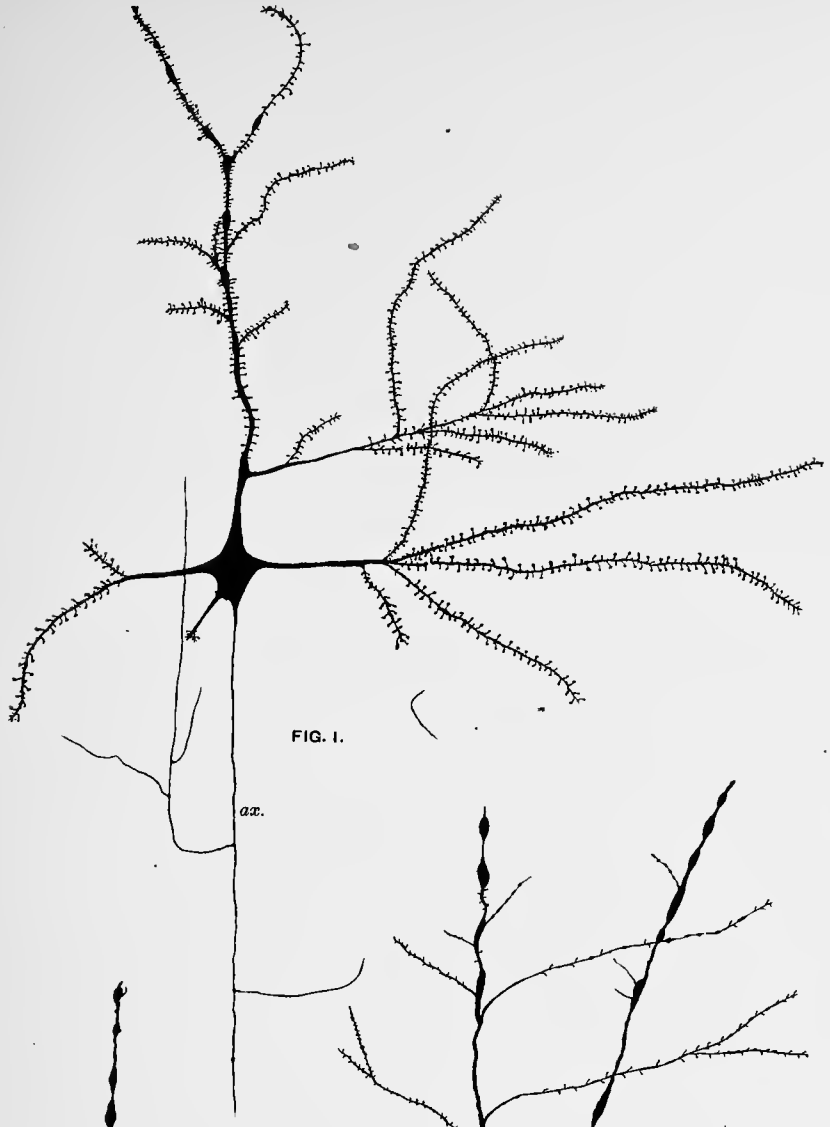

FIG. 1.

FIG. 5.

FIG. 4.

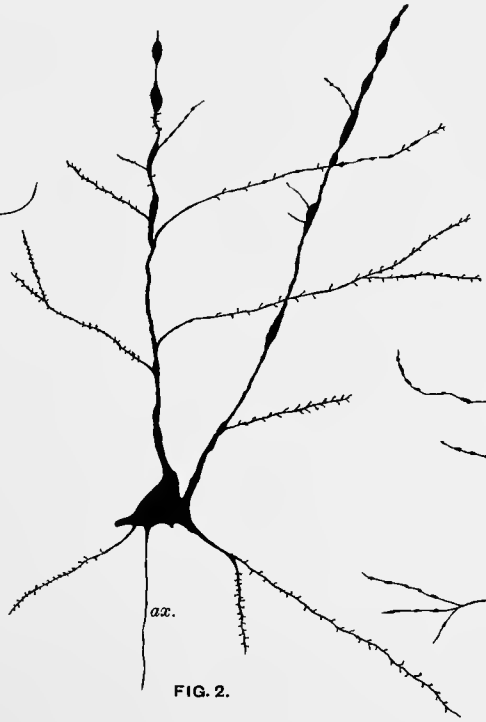

FIG. 2.

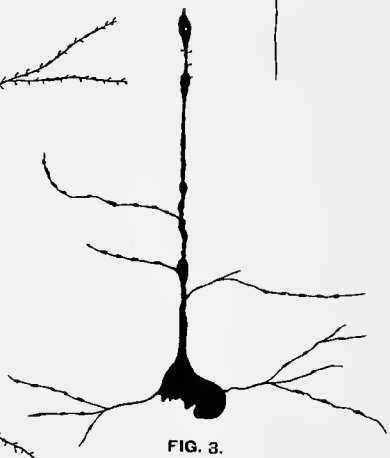

FIG. 3.

SERUM.

Allen & Co Lith Baltimore.

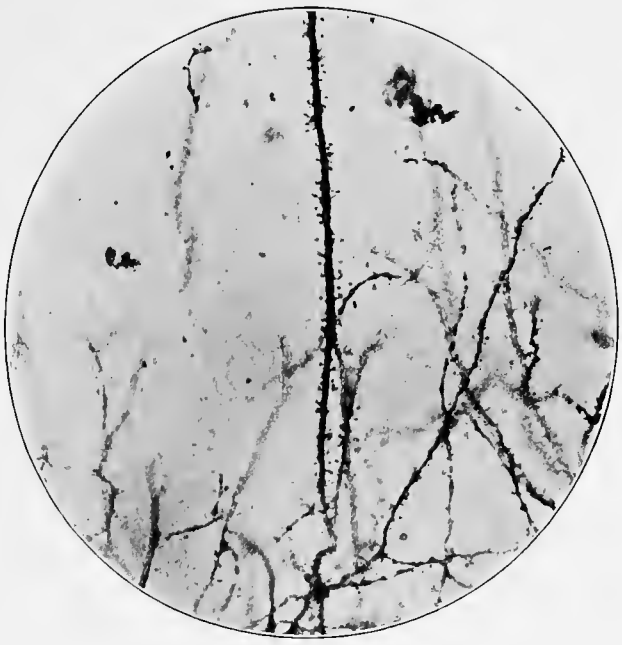

Fig. 6.

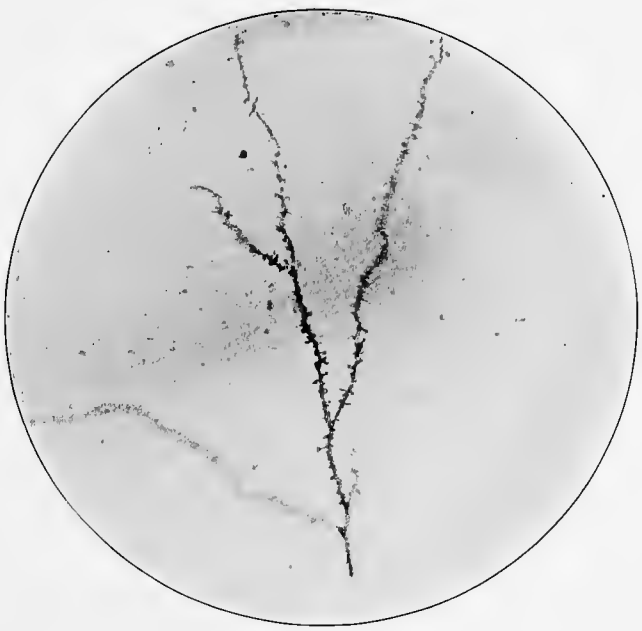

Fig. 7.

SERUM.

PHOTO. BY DR. A. G. HOEN.

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PART III.—RICIN POISONING.

Experimental Lesions produced by the Action of Ricin on the Cortical Nerve Cell of the Guinea-pig's and Rabbit's Brain.

Section I.—The Effect of Acute Ricin Poisoning.

Since the completion of the last article of this series on the condition of the nerve cell in serum poisoning, the two papers by Monti, above referred to, have appeared, showing lesions somewhat on the same order as those we have already seen in chronic alcoholism and serum poisoning, but in each separate one there is sufficient difference in the form and general deportment of the tumefactions, as well as in the relation of the gemmulæ to the morbid process, to enable an accurate observer to differentiate without difficulty in a well-stained slide from what pathological condition it was prepared.

Monti in his last article devotes a portion of a page to the gemmulæ, the first detailed notice of these important parts of the neuron that I have met with. He designates them as spines, describing them as having *en masse* the appearance of a bunch of moss covering the protoplasmic stem, and mentions that they are constantly to be found on the cells of the adult brain, the latter statement agreeing with what we have already determined.

A further consideration of the gemmulæ may not be out of place, and has a future bearing on the pathological conditions hereinafter described. In slides prepared according to the long Golgi method I have been unable to determine them with any constancy, and even with the ordinary osmium-bichromate fixing method of Cajal they are apt to be inconstant, at least in my experience. With the silver phospho-molybdate method they are constantly stained, are of fixed shape, according to the variety of cell from which they proceed, and are present on every kind of nerve cell in the cerebrum and cerebellum in varying numbers, but reach their highest development on the psychical and Purkinje cells.

Opportunity has hitherto not been afforded me to study their development after the beginning of extra-uterine life, but judging from the works of others, they do not seem to be present on the ganglion cells of the cortex until some time after birth; certainly some weeks in the lower animals (van Gehuchten, etc.). They are present on the protoplasmic prolongations of the pyramidal cortical cells (Cajal) of all vertebrates, but their deportment and expansion depend greatly on the animal from which the section is taken. Generally speaking, they are less prominent in the lower vertebrates, and reach their highest development in man. Even in the human being their numbers and luxuriance depend on the individual, for in persons of low mental grade they are not nearly so prominent as in better endowed individuals. Their development appears to depend largely on the receptivity of the species of animal to education from external impressions, dull vertebrates like rana presenting a wide difference from animals capable of receiving a higher education, as the dog; hence we are inclined to believe that there are certain inherent qualities in the development of the cerebral cells themselves that render one species of animal more capable of receiving and retaining impressions from extraneous sources than others; in other terms, they have memory for past events, and not only is the quality of the protoplasm different in one animal from another, but there are differences in the actual construction of the neuron itself.

Moreover, each psychical cell of the cortex possesses an individuality of its own, the shapes and general appearance of the cells differ widely, the general arrangement of the principal dendrites is different, the disposition of the gemmulæ varies slightly between each cell, the apical protoplasmic extensions are sometimes widespreading, sometimes do not expand into a number of branches until they reach the neighborhood of important nerve endings in certain well defined regions of the brain-rind.

A more extensive examination of histological specimens leads me to reopen and reconsider the question of the nodosities on the dendrites being normal, or artifacts from the deposit of fine precipitate on the dendrons giving them the appearance of being covered with nodes, as is the view taken by Flatau (Arch. f. mik. Anat., Bd. 44), already referred to in the preceding paper.

In early post-foetal life the dendrites are covered with varicose swellings that may persist over a variable time. In some adult animals these varicosities seem entirely to disappear (man, rabbit), while in others they are still persistent, though in very inconsiderable numbers (guinea-pig). Even when they are present in these animals they are always of very small size, present rather the appearance of irregularities than varicosities along the finest stems, especially toward their tips, and are covered, equally with the other portions of the stems, with the gemmulæ, and never encroach upon the thicker portions of the primordial or basal dendrites. That they are not artifacts is further evidenced by the fact mentioned in a previous paper, that under intense illumination they show none of the characteristic appearance of precipitate, but fine parallel lines converging on the unswollen portion of the dendron. Differences in the staining qualities of the cells are very much more puzzling than any deposit of precipitate and may occasionally lead to wrong interpretations.

All of our specimens were placed in the fixative fluid almost immediately after death, and accordingly I consider that we are able to exclude even the suggestion of post-mortem changes without further comment on this side question.

Hitherto in these studies we have had the absence of the gemmulæ from the swellings to aid us in determining whether we were observing a normal or abnormal nodule on a dendrite. In the present investigation, especially in the animals that lived but a short time after the injection of the poison, we no longer have this constant guide; for in the short space of a day and a half it could hardly be supposed that there would be complete destruction of these most delicate portions of the nerve body; and such indeed is the fact; though we do meet with a certain diminution of the pin-like attachments to the protoplasmic stems. To counterbalance this loss of control we find in the cases of pathological swelling the lateral buds pushed further apart from each other than is natural, and while often they may appear to be present in diminished numbers, an actual count will show that they closely approximate the numbers on the normal dendrites, though at times, when the swellings have considerably advanced, they perceptibly diminish. This condition is, however, only in the very earliest stages,

when alterations in the protoplasm have hardly begun; in further advanced stems they gradually disappear, until when the thicker portion of the primordial dendrite becomes involved in the swelling, which is never the case in normal preparations, they vanish rapidly. This retention of the gemmules is a strong argument against the tumefactions being artifacts, and clearly shows that the swelling comes from within the substance of the stem and pushes the gemmulæ, which are still adherent, outwardly and apart.

The researches upon the action of *ricin*, the amorphous poison obtained from the castor bean by Erlich and Flexner, induced me, after reading the paper by the last-named writer, to infer that this agent would be an excellent one to cause pathological alterations in the protoplasm of the ganglionic nerve cells.

Dr. Flexner very kindly placed at my disposal the brains from a number of his ricin rabbits and guinea-pigs, all fixed in Müller's fluid.

I cite in abridgment the lesions discovered by Flexner in the acute cases in tissues other than the nervous system: The lymph glands are everywhere throughout the body swollen and softened. The small intestines are distended and pale, their contents being glutinous, soft, grayish-white in color, and resembling in appearance cholera-stools. The patches of Peyer in both the small and large intestines are elevated, swollen and pale. The heart is filled with blood, the right ventricle especially being distended. The blood is fluid, or soft clots may appear. Neither the kidneys nor the lungs show especial alteration. The spleen is slightly swollen and softened; the liver is large, soft, and yellow in color.

The microscopical pathological alterations found in the viscera in the acute cases of poisoning are very profound. In the lymph glands hemorrhages are commonly present, and many of the lymphatic elements are necrotic, and fragmentation of the nuclei is common. The lymphatic apparatus of the intestine shows in an analogous manner the destructive influence of the poison, but cell death is much more extensive, and the swelling of the follicles is clearly due to the increase in the number of the lymphoid elements. The destruction is, however, not limited to the lymphatic elements in the follicles, but those in the villi suffer extensively and the epithelial elements are little spared. The spleen shows changes

similar to the lymph glands, and these are localized in part in the Malpighian bodies.

The liver presents the greatest variety of forms of cellular death. In the capillaries the endothelial cells are sometimes fragmented and necrotic, and the leucocytes suffer a similar change. But in the liver cells the process reaches its height. The yellowish areas visible to the naked eye correspond to foci of coagulation necrosis of liver cells. The liver cells in some of these areas are still preserved, but they are hyaline in appearance and devoid of nuclei, while in others the cells are much altered in appearance and staining properties, and the nuclei have undergone another form of necrosis. They have died as a whole, becoming paler and paler, until they finally refuse to stain, with apparently a synchronous alteration of the cellular protoplasm.

These foci of necrosis are often surrounded by large quantities of granular detritus. Some of the detritus must have come from emigrated cells, as we now know happens in these necrotic foci, where they suffer the same fate as the tissue elements.

The lymphatics in the interlobular spaces of the liver are choked with the nuclear detritus. Manifestly such an amount of nuclear material could not come from the cells lining the lymphatics nor from the cells of the lymph. There is only one interpretation of this process possible: it represents the nuclear detritus of the tissues and emigrated cells which had been swept by the lymph vessels into the current.

As it is not possible that such extensive changes should occur in the other tissues of the body without implication of the nervous elements, we obtained from Dr. Flexner the brains from six of the acute cases, and after hardening them carefully, further treated them after the silver phospho-molybdate method, and several nuclear stains, as in the former studies. For control material we used the fresh cerebra of a healthy full-grown rabbit and a guinea-pig, treated according to the same procedure as the pathological material, allowing them to remain exactly the same length of time in the hardening and staining media.

It will presently be seen in the description of the individual cases that in the five guinea-pigs the amount of destruction of the nerve elements depends not altogether on the amount of the

Condensed Table of the Acute Ricin Series.

No. in Series.	Animal used.	Age.	Weight.	Date of inoculation.	Death occurred in hours.	Amount of ricin	Clin. cause of death.	Gross anatomical lesions.	Remarks.
1	Guinea-pig.	Adult.	510 gram.	Aug. 31, '95.	36	1 mg. Subcutaneously.	Intoxication.	Usual lesions.	All the animals received the inoculations subcutaneously, with the exception of the rabbit, and with the usual precautions to avoid infection from extraneous sources. The inoculation was only made once in each case.
2	"	"	680 gram.	Sept. 4, '95.	40	0.5 mg. Subcutaneously.	"	Œdema and hemorrhage at site of inoculation.	
3	"	"	740 gram.	Sept. 4, '95.	48	0.25 mg. Subcutaneously.	"	Usual lesions.	
4	Rabbit.	"	1700 gram.	Aug. 30, '95.	14	1 mg. Intravenous.	"	"	
5	Guinea-pig.	"	700 gram.	Sept. 8, '95.	72	0.125 mg. Subcutaneously.	"	"	
6	"	"	450 gram.	Oct. 10, '95.	37	1 mg. Subcutaneously.	"	"	

poison injected into the system of the animal, but also on the duration of the poisoning. Almost equal changes can be produced in seventy-two hours by the inoculation of 0.125 milligramme ricin as by the inoculation of a whole milligramme lasting over a period of only thirty-six hours, and perhaps had the animal lived a still longer time the changes would have been even more pronounced. On the other hand, in the single rabbit subjected to an intravenous inoculation with 1.0 milligramme ricin the destruction of the protoplasm of the nerve cells was greater than in any other case, though Dr. Flexner informs me that he has always noted greater intensity of the action of the toxine in intravenous than in subcutaneous injections.

The Effects of the Toxic Substance Acting Directly on the Substance of the Nerve Cell.

(a) *Lesions seen by Nuclear Stains.*—The study of the two cases selected (Nos. 2 and 4) for examination of the blood-channels' walls with nuclear dyes shows lesions entirely similar to those found by Flexner in the abdominal organs, only not of such intensity. In the finer vessels there are many places in which the endothelial nuclei are swollen, receive the stain badly or not at all, and are occasionally necrotic and fragmented. The perivascular channels contain considerable amounts of a fine-grained detritus that does not take up any other dye than eosin, and this only in sufficient quantities to give it a pale rose tint. This detritus is to be found in the spaces around all the medium-sized and larger blood-vessels, and the amount of it is in places sufficient to retard the lymph currents. All evidence of the presence of thrombi in the smaller vessels is absent, and the numbers of white blood corpuscles within the vessels and perivascular spaces are inconsiderable.

The protoplasmic bodies of the majority of the nerve cells appear to be unaffected by the poison, a few seem to be breaking up into granular matter. Very curious nucleolar figures are to be seen everywhere in the nerve cells of the gray substance. The fine dust-like granules and the two or three larger particles that are normally present are no longer to be seen, but in their place in the interior of the nuclear ring lies a brightly stained irregular mass, sometimes of horseshoe outlines, or at others of varied shape,

probably composed of the aggregations of the nucleoli and nucleolar dust. (See section "Nucleolar Changes.")

(b) *Lesions seen by the Silver Phospho-molybdate Method of Staining.*—The six cases divide themselves, so far as the intensity of the destructive influences determined by the drug are concerned, into two principal groups: those in which the pathological alterations are limited to the finer branches of the cell, there obtaining fine swellings of the outermost portions of the protoplasm of the cell accompanied by but little denudation of the gemmulæ, and the remaining portions of the cell are free from apparent injury; and, secondly, cases in which there is involvement of the dendrites down to the cell body, with great disappearance of the lateral buds, and certain changes in the corpus of the cell.

The first detail is to be found after the continued action of the drug for comparatively short periods of time; the second, either after the long-continued action of such small doses of the toxic substance as will enable the animal to survive a considerable number of hours, or, after throwing into the circulation of a proportionately very considerable amount to the weight of the animal of the toxine, inducing a sudden and intensely destructive effect upon the cerebral cells (cases 4 and 6).

All the cells of the cortex besides the fusiform and angular cells of the outer layer, which stain infrequently, are, irrespective of the anatomical situation of the different layers, involved in greater or less degree by the degenerative process; but as the pyramidal cells of the second are the most numerous, best defined and important, we shall, as hitherto, take them as the sole type of cortical cell in which degenerative changes are apparent, if only from the fact that their greater constancy in receiving full impregnations with the silver salt renders one less liable to be wrongly influenced by irregularities in the staining qualities.

In the first class we find on the tips of the dendrons, particularly those situated within the limits of the molecular layer, well defined, rounded, irregular, and fusiform swellings, which appear to begin toward the extreme outer endings of the protoplasm and gradually extend downwards (Fig. 1). On these tumefactions the gemmulæ may or may not be involved. When the swelling looks comparatively recent the gemmulæ do not seem to be greatly diminished in num-

bers, but when they are older they disappear. That the swelling commences in the substance of the dendritic stem is evidenced by the circumstance that the lateral buds are pushed apart at first, before they begin to atrophy and disappear, and then undergo a change that is not well defined by the silver impregnations. They absorb less of the staining material, are yellowish in color instead of black, and then, before any other definite alteration takes place, they fall off the stem, and presently the detritus is taken up by the lymphatics of the brain and they vanish entirely. As the diameter of the gemmule does not exceed one-tenth that of a red blood corpuscle, it is quite easy to understand that they may be very rapidly absorbed by the lymphatic apparatus and quickly lost. It is not uncommon to see a few of them lying in the tissue close to the side of the swollen stem but without any visible connection with it, and from the extreme tenuity of their attachments to the protoplasm of the stem, and the dependence upon it for nourishment, it may be readily understood that the slightest injury affecting the vitality of the parent dendrite will instantly cause an involvement of the side buds of the branches. When the swellings become fairly numerous (Fig. 2) along the finer dendrites, the stripping off of the buds soon becomes very apparent.

In these earlier cases there is little atrophy of the stem in the intervals between the tumefactions, the gemmulæ being retained in but slightly diminished numbers and showing only occasional variations in the staining. The thicker dendrites are in the first class rarely, if ever, involved, nor does the cell body lose any of the definite sharpness of contour or appear swollen or malformed.

The basal dendrites seldom participate to any extent in the first steps of the tumefactive process, though one is occasionally seen with a small swelling along the course of one of the branches; but this is exceptional.

The axons from all the cortical cells display none of the irregularities in their outlines or abnormal increase in the number of varicosities that have been described in the more chronic diseases. Likewise the collaterals are equally finely contoured, and the bulbous endings situated upon short lateral branches arising from the principal fibres are all well stained, and have every appearance of being healthy.

Fibres coming from the deeper layers, axons from the cells of Martinotti, diffuse meshworks from the intermediary cells are all well impregnated and present no difference from those in control preparations.

Neuroglia changes seem in the earlier cases to be absent. It is true that the staining, in the first series of sections, of the different varieties of support cells was not very good, only scattered ones being visible occasionally in the field, but those stained presented every appearance of health.

No coarse lesions were visible in the walls of the blood-vessels in cases 1, 2 and 3, with the exception of an inconsiderable number of perivascular extravasations in the second case. Even in the hemorrhages the blood corpuscles were perfectly preserved, showing that they took place about the time of the exitus.

In the cerebellum, in the first class of cases, we have met with but imperfect staining of the nervous and support elements, the Purkinje cells and Bergmann fibres excepted.

The aspect of some of the last-named nerve cells is exceedingly instructive. In the first place they present the usual mixture of perfectly normal and damaged cells, in a similar manner to the cellular layers of the cerebrum. A damaged cell may have some of its branches entirely sound, while others have lost the greater number of their gemmulæ, and have very ragged outlines (Fig. 12). There is now very little irregular tumefaction of the protoplasm of the stems, but on the other hand an apparent thinning, seemingly due to the stripping off of the gemmulæ.

An occasional basket-cell with its peculiar axon is now and then well stained; some of them show alterations of the dendrons, some do not do so, but the nerve extension is always normal. In the molecular layer nothing is stained beyond certain nerve fibres, and in the central core of the leaflet, in addition to these, a few short-rayed neuroglia cells. The Bergmann support cells of the molecular layer afforded from their constant staining opportunity for accurate investigation of their structures, but gave no indication of any degenerative process affecting them.

The changes found in the nerve cells of the second class of cases are relatively much more interesting from the greater intensity of the alterations found, as well as the absolute pathological signi-

ficance they possess. It is always to be remembered, however, that except in one case (No. 6) there was nothing approaching an involvement of all the neurons of the cortex, but that actually a large proportion of cells in all portions of the layers has every indication of health, and while very extensive alterations are found in very many of the neurons, those that are normal and those that belong to the first class greatly outnumber them.

In every section taken from cases 4, 5, and 6, we see numerous pictures corresponding to Figs. 3 and 4. Practically the neuron is reduced to the main apical dendrite, with sometimes a few of the basal ones remaining intact, sometimes they are degenerated. The apical dendrite is shorn entirely of the lateral branches, or they are reduced to irregular filaments; the outspreading uppermost branches vanishing completely. The tree-like form has departed, it is reduced to a trunk ill-shapen and knotted, and its roots are dying. Along the stem of the trunk we find swellings of various sizes and shapes; within the interval between the swollen portions, lines of protoplasm much thinner than at corresponding points in normal specimens. When we look for the gemmulæ we find they are still present in some places, in others they are entirely absent, but as a whole their numbers are greatly diminished, the remaining ones ofttimes appearing to be badly stained. In the most advanced of these instances the cell body appears not quite as angular as in the control specimens, but otherwise there is no definite alteration.

Turning from these middle forms to others that have suffered more considerably in the atrophic process, we find an extensive reduction in the length of the apical and basal dendrons. Some of these are thinned to a great degree, but have few tumefactions (Figs. 5 to 10), but others have numerous swellings of all sizes, both in the apical and basal dendrites, the primary ones always showing the greater amount of tumefaction and atrophy. There is still retention of very limited numbers of gemmulæ. Quite often, however, there is entire absence of them over certain of the stems, which now appear thinned to fine filaments, with the remains of a nodule showing at intervals.

In the most degenerated type the basal dendrites are reduced to stumps, the primitive one is atrophied down nearly to the body

sels, which conduce and augment the direct action of the poison. Overwhelming destruction of the cellular protoplasm, rendering the lymphatic apparatus unequal to cope with and remove the detritus of the cells, may also become an important factor, as the more products of the dead tissues that remain in close proximity to the living ones, the more rapid, presumably, is the destruction of the remaining living elements.

The action of the drug is proportionate to the amount of it injected into the body of the animal, also to the duration of the poisonous action before death occurs. Limited quantities continued over a considerable time exercise the same destructive action as more extensive doses acting during a few hours.

The fine extensions of the cells are first destroyed, later the thicker ones, lastly the cell body and axon, both of which resist the process for a long period.

The question of regeneration of the nerve elements in animals that may survive the deleterious influence of a poison is of the first importance from a clinical standpoint in the future history of patients suffering from severe infectious diseases, but of this we have at present no data. We are, however, led to expect from the history of such cases in the human being that there is at least a partial regeneration of the nerve elements, though in such instances as I have had the opportunity of examining the recovery is far from complete.

Special Description of the Separate Cases.

No. I. Guinea-pig weighing 510 grammes, inoculated with 1.00 mg. ricin, died in 36 hours. The brain of this animal did not harden well in the preservative fluid and it was therefore discarded.

No. II. Guinea-pig weighing 680 grammes, inoculated with 0.5 mg. ricin, died in 36 hours. There are no coarse vascular lesions visible in the silver slides. The disks of the red-blood corpuscles, except in a few instances, are distinct and unchanged. In the capillaries are single rows of the blood corpuscles very closely packed together; everywhere there is evidence of antemortem hyperæmia. In two sections, single, small, perivascular hemorrhages were found at about the juncture of the molecular

and second layer of the cortex. In every region examined there is evidence of turgescence and congestion of the smaller arteries and veins.

Definite lesions of the neurons are not extensive, and relate almost entirely to the parenchyma of the primitive and basal dendrites. The most common alteration found is that the lateral branches of the pyramidal cells within the molecular layer are studded with considerable numbers of swellings of various sizes and shapes, but without any considerable diminution in the numbers of the lateral buds. Occasionally a whole branch is so studded with these tumefactions as to form a striking object under low power, but this is rare.

In a considerable number of the cells the tumefactions are not confined to the finer dendrons within the molecular layer, but spread downward toward the lower portions of the primordial process, and such cells may be found in sparse numbers in all portions of the gray layers. When the stem of the primitive dendron is affected in this manner there is an evident though slight decrease in the number of the gemmules, and also a more apparent change in the disposition of the finer branches coming off from it; they seem to be less numerous than normally, and in those that remain the lateral buds are less luxuriant than usual, though they still stain fairly well and possess all the attributes of the normal buds except numbers. The swellings on the primitive or basal dendrites have the buds present, but they are usually more widely separated than on the natural stem, which is, presumably, accounted for by the tumefaction of the substance of the dendron pushing them more widely apart. As already stated, it is customary to find a distinct diminution of the buds on much swollen dendrons.

The lower portion of the main apical dendrite is never involved in this case, indeed lesions of the principal branches anywhere in the vicinity of the cell body are extremely rare. Decided alterations of the corpora are entirely absent. Variations from the normal in the axons were not made out, though the staining of this portion of the neuron with the collaterals was often superb.

The tendency everywhere is for the altered cells to be scattered at intervals with large numbers of normal ones in between them; large areas of a section may be gone over without finding any traces of a diseased cell, then numbers of altered ones are seen

among the normal; altogether the proportion of diseased neurons in the second case is by no means numerous. There are no distinct lesions of the neuroglia elements, though, possibly, some swelling of the bodies of the vascular cells may be found.

In the cerebellum there is distinct loss of the gemmulæ on the branches of some of the Purkinje cells, combined with more or less irregular swelling of the stems, but these alterations are not numerous. The corpora and axons remain intact. The various fibres coming to and fro from the granular layer have no alterations in them as far as they are impregnated. The granules do not stain at all.

No. III. Guinea-pig, weighing 740 grammes, inoculated with 0.25 mg. ricin, died in 48 hours. Equally with case II there is nothing of considerable interest concerning the larger blood-vessels or their contents beyond the fact that there is a certain degree of hyperæmia of the entire rind of cerebrum and cerebellum, but nowhere is it sufficient to have occasioned great diapedesis of the blood corpuscles.

The appearance of the nerve elements does not differ materially from that of case II, though the destruction of the branches of the dendrons is more frequent, all portions now being frequently involved, also the number of the primordial stems that are implicated in the destructive process is greater than in the other example.

The gemmules along the stems are somewhat sparser, and among those still retained there are some that are pale, ill-stained, and look as if the morbid process had already begun in them. The cell body is never frayed or eroded, yet the contours of the cells are slightly changed, as their angles, particularly those having the most damaged dendrons, are more rounded than is seen in normal preparations. Changes in the neuroglia elements are, so far as those impregnated indicate, very slight in the cortex of the cerebrum and cerebellum.

In the last-named organ the alterations in the Purkinje cells are on the same order as in the previous cases, namely, focal alterations of a few cells here and there, with the majority remaining intact.

There are no variations from the normal in the appearance of the fibres and their collaterals, nor are there distinct differences between the control neuroglia cells and those in this case. It is

possible the vascular cells are a little swollen, but the difference is uncertain.

No. IV. Rabbit, weighing 1700 grammes, intravenous inoculation with 1 mg. ricin, died in 14 hours. The blood-vessels in this case are far less congested than in those preceding it, the arterioles are empty as a rule, but the veins contain a small amount of blood, in which the red corpuscles are distinct, with their outlines perfectly preserved. The lesions of the blood channels, as seen with nuclear stains, have been given in the first part of the article, for cases IV and VI.

The destruction of the protoplasmic branches of the cells is far greater than in any of the previous cases, and in many instances there is complete atrophy of all the branches nearly down to the cell body, while in a host of others there is implication of the finer and coarser dendrites as well as the primordial stem. The loss of the gemmulæ is exceedingly great, many cells advanced in the degeneration only showing a half-dozen of them over the entire series of branches. The tumefactions are also larger and more numerous, altogether the process is more intense than anything we have met with in this series.

Besides a rounded appearance of their contours, the corpora of the cells show little alteration; one or two had what appeared to be an erosion near the nucleus and extending into it, but this is probably an artifact produced by the saw-like cutting action of the knife when the sections were made. Some of the dendrons of the several varieties of cells in the cortex show a beaded arrangement of the protoplasmic twigs (Fig. 11), with complete loss of the lateral buds; literally every gemmule is absent from the dendrite, a different condition from anything we have before remarked in any of the sections. In these cells small varicosities appear at almost equal distances along the protoplasmic stem, which are tinged intensely black by the silver salt. In the intervals between the swellings the stem of the twig appears to have atrophied, not only in the long direction of the stem, but also in its transverse diameter. Lateral branches seldom come off from these thinned twigs, and their whole appearance is indicative of an atrophic alteration in the protoplasm.

The question arose as to these cells being due to imperfect stain-

ing, as none of them are throughout equally well impregnated in the intervals between the beads, especially the small ones on the finer remaining stems; and the protoplasm is ofttimes almost untinged. These cells are to be seen among groups of well-stained cells, accordingly it is hardly possible that a single cell could be incompletely stained when others surrounding and overlapping it with their dendrons are well tinged both in body and dendrons.

In the cerebellum the alterations are very considerable, the gemmules are stripped off numbers of the Purkinje cells as an entirety, the branches are bare, but there are no large numbers of local swellings on the stems. The small cells of the molecular layer show modifications of the same changes, and their gemmules are not tinged in great numbers.

The nerve fibres seem to be entirely unimpaired in any way, either in the cerebrum or cerebellum, both in respect to their continuity or change in the contour of the cylinders themselves. The collaterals, to their bulbous terminations, could often be traced, while some exceedingly beautiful examples of the outspread of the axons of the intermediary cells were found and traced to their endings, after large numbers of bifurcations. The *grimpante* fibres of Cajal in the cerebellum were particularly distinct in this specimen, as were likewise the axons of the Purkinje and basket cells.

The alterations of the neuroglia are similar to those found in case VI, and are described more in detail under that heading.

No. V. Guinea-pig, weighing 700 grammes, inoculated with 0.125 mg. ricin, died in 72 hours. Inoculation subcutaneous. While the action of the drug upon the protoplasm of the dendrites is not so grave as in the preceding instance (No. IV), the lesions are of equal importance, marking the fact that not only does an overwhelming dose of the poison produce grave alterations of the protoplasmic substance, but that the effects of small doses continued over longer periods are equally injurious. The damaged cells are no longer scattered between comparatively normal ones, but are to be found everywhere, and the proportion of absolutely normal neurons is reduced to a minimum, indeed this is so well marked that one has to observe right carefully to find an approximately normal cell. The basal dendrites are as equally implicated

as the apical, and many of them are also knobby and atrophic down to the thickened portions of the stems.

The lesions are, as an entirety, of the same general character as in the preceding instances, but there is less of the moniliform swelling of certain of the dendrons, with total absence of the gemmulæ, as was the case with No. IV.

The gemmulæ are accordingly retained in greater numbers on the swollen spots on the dendrons, while there is less thinning of the stems themselves. No cells were present with destruction of the corpora, but many were seen that certainly exhibited greater roundness of the bodily contour than is customarily found.

In the cerebellum the lesions are very well marked, the swellings of the stems and the loss of the gemmulæ are well shown, the small cells of the molecular layer and the Golgi cells of the granular have their prolongations swollen and irregular, and everywhere there are very decided changes.

The staining of the nerve fibres of all descriptions was in this case especially fine, and a careful study was made of them. In the cortex, the axons of the projection cells were finely tinged, very regular in contour, but an occasional varicosity showing at the juncture of a collateral or in the course of the fibre, but nothing abnormal. The ascending fibres from the cells of Martinotti were traced to the outer layer without difficulty; the net-like arrangement of the axons of the intermediary cells was very distinct, and the branches could be traced to their bulbous knobs.

In the cerebellum the tingeing of the fibres was equally good, the *grimpante* fibres of Cajal were numerously stained, likewise were the axons from the basket cells of Koelliker with the peculiar endings encircling the bodies of the Purkinje cells; also the axons from these last cells were well marked and were without varicosities.

The staining of the various forms of the neuroglia is similar to that in the last case. The vascular glia cells are certainly swollen, the bodies and arms being more prominent than usual, but the other varieties have no evidence of morbid alteration.

No. VI. Guinea-pig, weighing 450 grammes, inoculated subcutaneously with 1.0 mg. ricin; death occurred in 37 hours Naturally from the overwhelming dose of the poison injected into this small animal the lesions found were very extensive and widespread.

There is great destruction of the fine branches and thicker stems, with great numbers of the bead-like swellings stretching over all portions of the stems and branches of both the apical and basal prolongations. Few swellings have any considerable size. The loss of the gemmulæ is very great, many of the injured cells have not a single bud upon them, while in others, and these are only present in small numbers, the gemmulæ are still visible, but are not equally or well stained. Even in the cells that retain something of the normal appearance it is very evident that the destruction of these delicate portions of the neuron has already begun, and that complete disappearance is only a question of a few hours' additional time.

In every portion of the cortex, and throughout every section that was examined, the same extensive destruction of the nerve cells prolongations was found. Absolutely no alterations in the contour or general appearance of the corpora of the cells could be determined, not even the rounded outlines of the cells subjected to the longer action of the poison could be found, all the pyramidal cells and the other nerve bodies retaining their usual angularity of contour and outline.

In the cortex the nerve fibres, with the exception of the descending axons of the psychical cells, did not stain well. The latter were tinged to some distance from the cell body and exhibited no irregularity or other departure from the customary contours.

Differing from the first three of our cases, the neuroglia structures were fully impregnated in all portions of the white and gray layers. Along the outer edges of the brain-rind the staining of the different varieties of support cells peculiar to this region is almost perfect, while all through the cellular layers there are here and there, as in good histological preparations, staining of isolated cells, but in contradistinction to these there is staining of only one variety, the vascular neuroglia cell; no long or short-rayed cells appearing, even in the white tissues, where usually they alone are impregnated.

These vascular neuroglia cells are large, the bodies seem of greater diameter than usual, are rounded, even globular in form, and the tentacles and short lateral projections are very coarse and distinct, seemingly swollen. The individual cells do not cover greater areas than is common among such cells. The reason why

the short and long-rayed cells do not impregnate is of course unknown, but I have in exceptional instances found the same peculiarity in normal slides, and regarded it as being due to some defect in the hardening process, though in these normal preparations it is not usual to find the same numbers of vascular neuroglia cells in the medullated tissues.

In the cerebellum there was, in accordance with the alterations in the cortex, similar ones in the Purkinje cells, with much destruction of the gemmulæ and swelling of the protoplasmic stems (Fig. 13), but these changes are to some extent focal, or rather not so universally diffused as in the cerebrum. Numerous Golgi intermediary cells in the granular zone, basket cells, and small angular cells in the molecular layer were all well defined, and some exquisite examples of the terminations of the basket cells were seen, but showed no alterations of their structures. The axons of the Purkinje cells only stained infrequently, and did not show any alterations. The resistance to the effects of the poison is therefore probably greater among the elements of the cerebellum than in the cerebral tissues. The peculiar bushy neuroglia cells of the molecular layer only among all the neuroglia elements of this region stained, but showed no ascertainable lesions either in the bodies or extensions.

The cerebral vessels showed very little congestion. The blood corpuscles were perfectly preserved, in the capillaries there was a single row, not closely pressed together.

Description of the Drawings.

Fig. 1. Psychical cell from the second cellular layer of the cortex, showing a few pathological tumefactions on the uppermost branches of the apical dendrite. Otherwise the cell is normal. Ricin poisoning of 36 hours' duration. Subcutaneous injection of 0.5 milligramme ricin.

Fig. 2. Projection cell from the second layer of the cortex, showing an increased number of pathological swellings on the finer stems of the cell. There is now distinct diminution of the gemmulæ wherever the swellings are found. Ricin poisoning of 48 hours' duration. Subcutaneous injection of 0.25 mg. ricin.

Fig. 3. Projection cell of the long apical process variety, showing numbers of large swellings of the protoplasm of the apical

dendrite, thinning of the protoplasm of the stems in the interval between the nodules, and considerable loss of the gemmulæ along the margins. The lateral branches have mainly disappeared. The basal processes are retained intact. Ricin poisoning of 72 hours' duration. Subcutaneous injection of 0.125 mg. ricin.

Fig. 4. Long apical process pyramidal cell with extensive swellings, chiefly fusiform in character, along the trunk, with entire destruction of the lateral branches and very great atrophy of the lateral buds. Ricin poisoning of 14 hours' duration. Intravenous inoculation of 1 mg. ricin.

Figs. 5, 6, 7. Small pyramidal cells of various shapes in different stages of degeneration. Ricin poisoning of 14 hours' duration. Intravenous injection of 1 mg. ricin.

Figs. 8, 9, 10. Larger pyramidal cells from the second layer of the cortex in advanced stages of degeneration. The cells, especially the last two examples, have lost the angularity of their contours. Ricin poisoning of 14 hours' duration. Intravenous inoculation of 1 mg. ricin.

Fig. 11. Pyramidal cell from the second layer, showing a beaded arrangement of the dendrons with much thinning of the stems. Ricin poisoning of 37 hours' duration. 1 mg. of the poison injected subcutaneously.

Fig. 12. Small branch of a Purkinje cell with two branchlets, the right one approximately normal, the left one ragged and with great loss of the gemmulæ. Ricin poisoning of 36 hours' duration. Subcutaneous inoculation of 0.5 mg. ricin.

Fig. 13. Small branch of a Purkinje cell, showing thickening and irregularity of the protoplasmic stems with entire loss of the gemmulæ. Ricin poisoning of 37 hours' duration. Subcutaneous inoculation of 1 mg. ricin.

All drawings were made with Zeiss, ocular 4, objective DD, enlarged.

PHOTOGRAPHS.

Fig. 14. Pyramidal cell from the second layer of the cortex in an advanced stage of degeneration. Acute ricin poisoning of 14 hours' duration. Intravenous inoculation of 1 mg. ricin. Enlarged about 500 diameters.

Fig. 15. Dendrons of the mid-portion of the second cellular layer, showing swellings and diminution of the lateral buds. Ricin

poisoning of 37 hours' duration. Subcutaneous inoculation of 1 mg. ricin. Enlarged about 500 diameters. Photographs by Dr. A. G. Hoen.

Section II.—The Effect of Chronic Ricin Poisoning on the Cortical Nerve Cell.

I have only been able to obtain a single brain from a case of chronic ricin intoxication. The examination of this cerebrum was, however, very satisfactory and definite, and as it is at present impossible to obtain more material, I have concluded to utilize the single case to complete this section of the series.

The 400-gramme guinea-pig was inoculated by Dr. Flexner on September 11th, 1895, with 0.03125 mg. ricin, subcutaneously. On the 18th day of the same month it received a like quantity of the poison, and on the 23rd instant it received an additional one-eighth mg. Death took place on November 7th, general emaciation being the best marked clinical feature of the course of the poisoning.

The principal anatomical differences between the acute and this chronic case lie in the size of the abnormal swellings upon the dendrites. Large numbers of small and medium-sized nodes are scattered upon the branches, but among them are some that have attained three or four times the size of the largest ones in the acute forms, and attract immediate attention. The vascular system does not appear to have suffered much in this case, there being no evidence of extensive congestions and dilations of the perivascular spaces with exudation of the lymphoidal elements.

The cerebrum was treated precisely according to the formula laid down in the preceding section and stained by the silver phosphomolybdate method, but no alcohol sections could be prepared for the Nissl treatment.

The staining of the nerve elements and neuroglia was fair, and frequent tumefaction of the dendrons and loss of the gemmulæ were found, but the diseased cells were by no means as extensively distributed among the sound ones as in the acuter forms, and the proportion of the sound cells is vastly greater. It is perhaps only every third or fourth dendrite in which we have definite departures from the normal. The tumefactions present the difference from the acute form in that the individual swellings are of greater size

and the primordial stems have fewer of the fusiform tumefactions extending through the length of the dendrite.

Wherever there is swelling there is loss of the lateral buds in very pronounced degree, sometimes extending to complete ablation of these portions of the cell, at others a small number are retained adherent to the parent stem, but they do not fully receive the stain in the finer portions of the gemmule attached to the lateral aspect of the cell branch.

The stouter stems, near the cell body, do not show any considerable variation from the normal. The corpora have nothing of the rounded swollen form noticeable in the cases in which death resulted from an acute toxæmia, but, on the contrary, their outlines are sharply defined.

The vast majority of the axons and collaterals from the projection cells show nothing abnormal. When the filaments are of extreme tenuity there are occasional breaks in the staining over short distances, then it recommences further on, and is then continuous over some short distance, only to be again broken. These variations of tingeing we consider due to an imperfect impregnation of the nerve fibre, and not a pathological condition. The terminal branches and the bulbous end-apparatus only stain infrequently, but wherever visible show the normal appearances by the phospho-molybdate method.

The bodies of the mossy neuroglia cells are larger than normal, rounded, sometimes globular in outline, and the tentacles are thickened and knotty. There are general evidences that these structures of the lymphatic system are undergoing modifications of a pathological nature. The support neuroglia of various kinds show no lesions.

Alterations in the cerebellum are upon the same order as in the cortex of the hemispheres, though not so well marked, the Purkinje cells, for instance, showing only occasional tumefactions of the branches and seldom any considerable loss of the gemmulæ. The nerve fibre structures do not appear to be implicated in the lesions. It is apparent from the results of the last three studies that the cerebellar structures have a greater resistance in their cells to toxalbumins and toxines in general than the cerebral. Whether this is owing to a difference in the blood supply, as has been suggested, is conjectural.

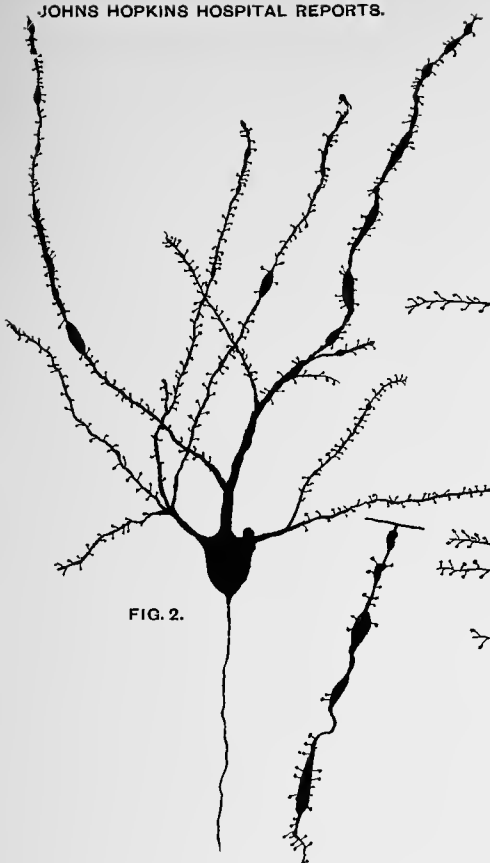

FIG. 2.

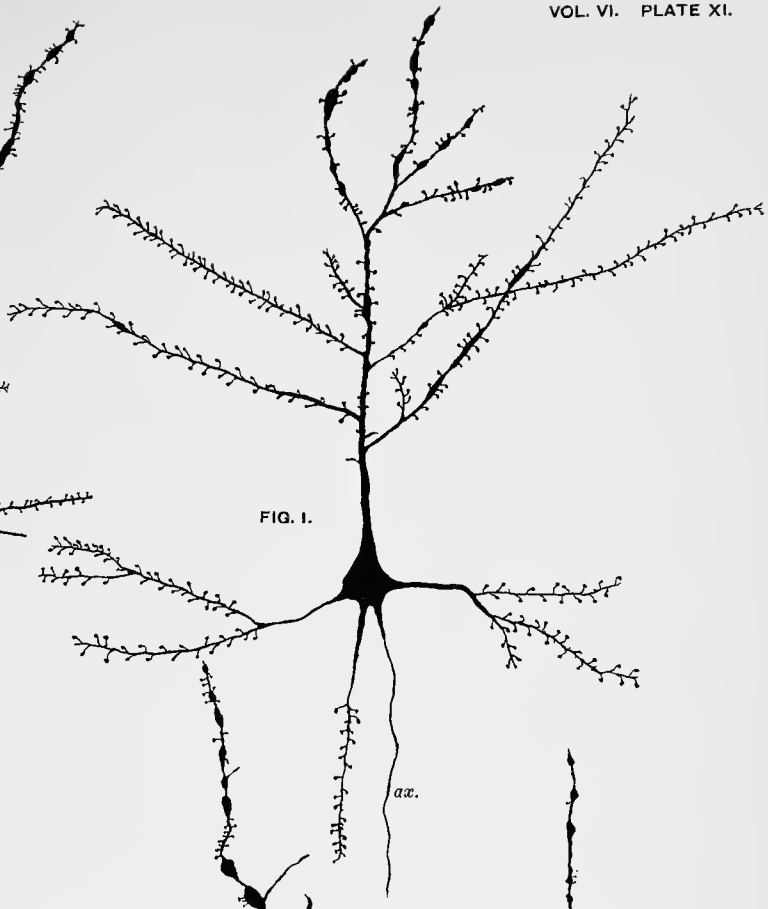

FIG. 1.

FIG. 3.

FIG. 4.

FIG. 5.

RICIN.

A. Hoen & Co. Lith. Baltimore.

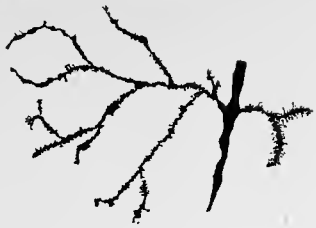

FIG. 12.

FIG. 13.

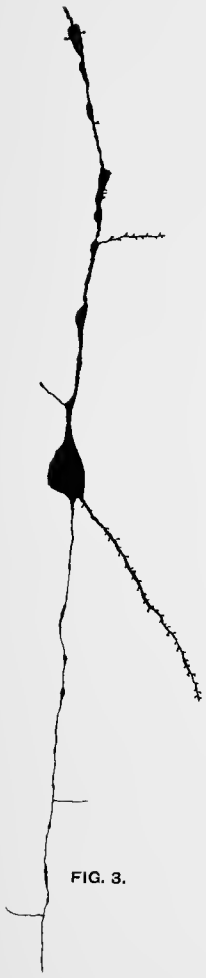

FIG. 3.

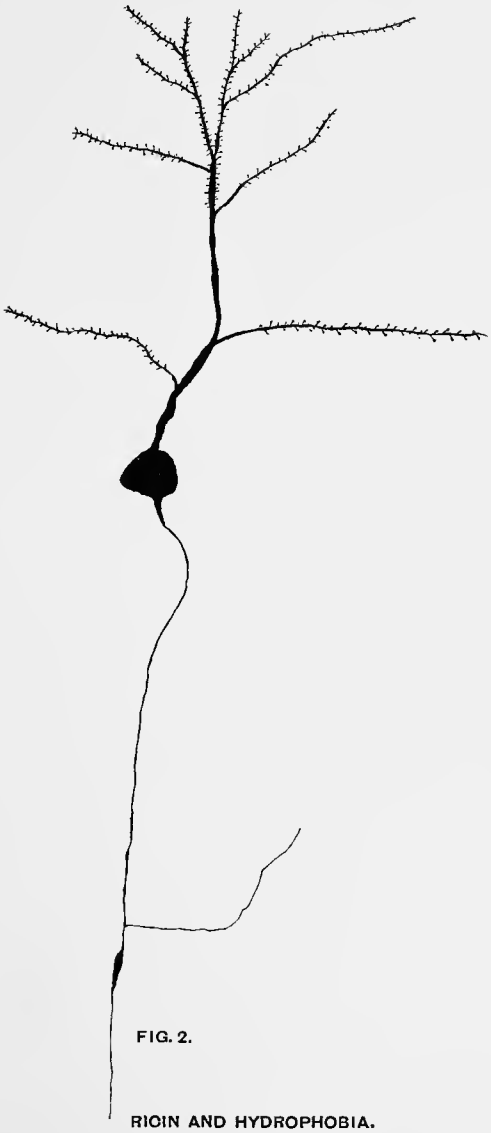

FIG. 2.

FIG. 1.

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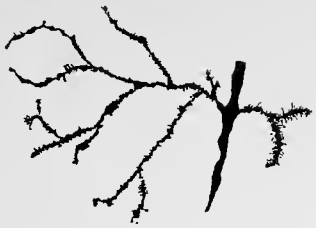

FIG. 12.

FIG. 13.

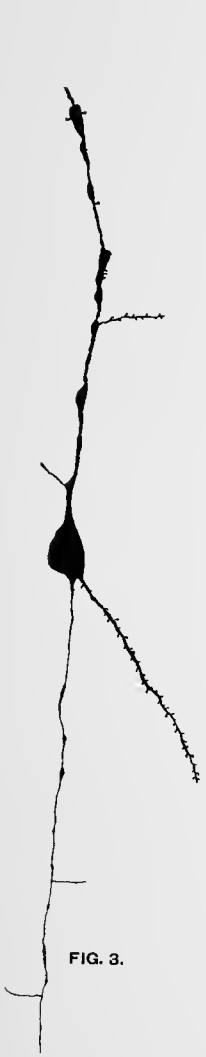

FIG. 3.

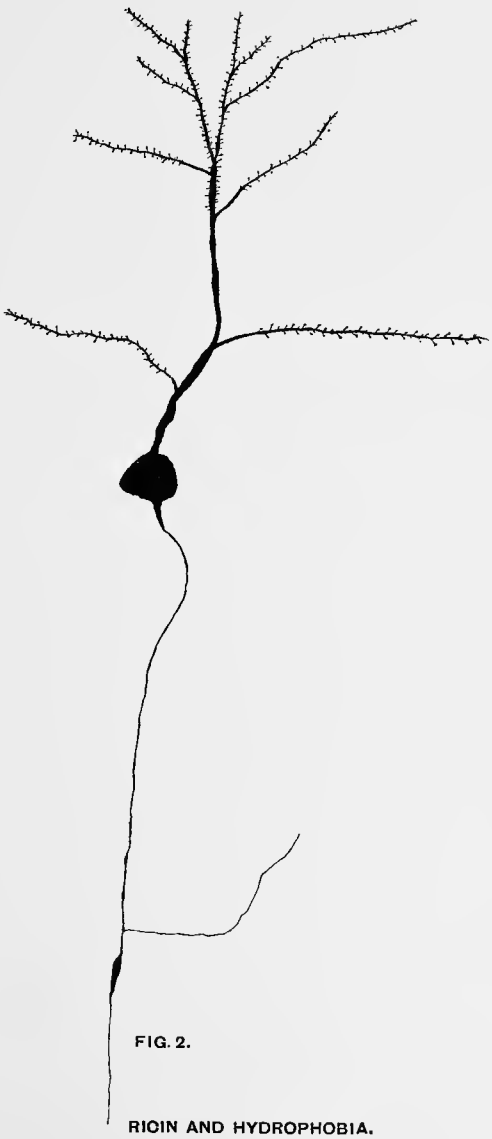

FIG. 2.

FIG. 1.

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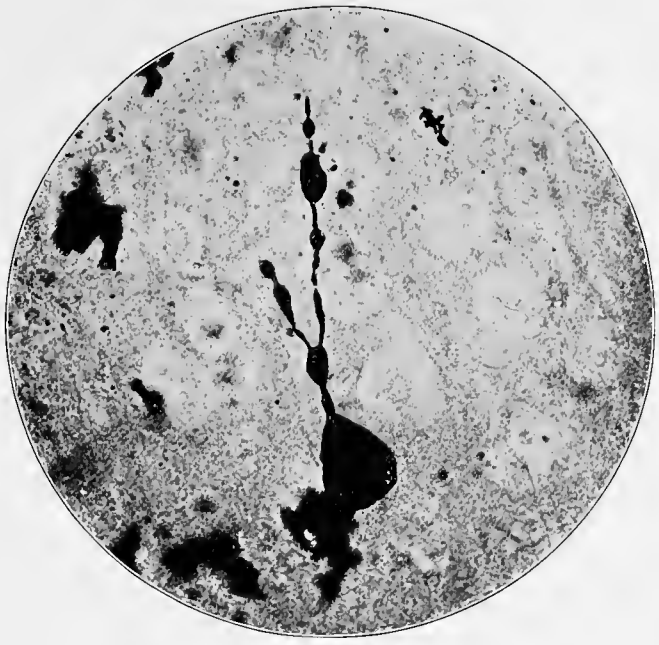

Fig. 14.

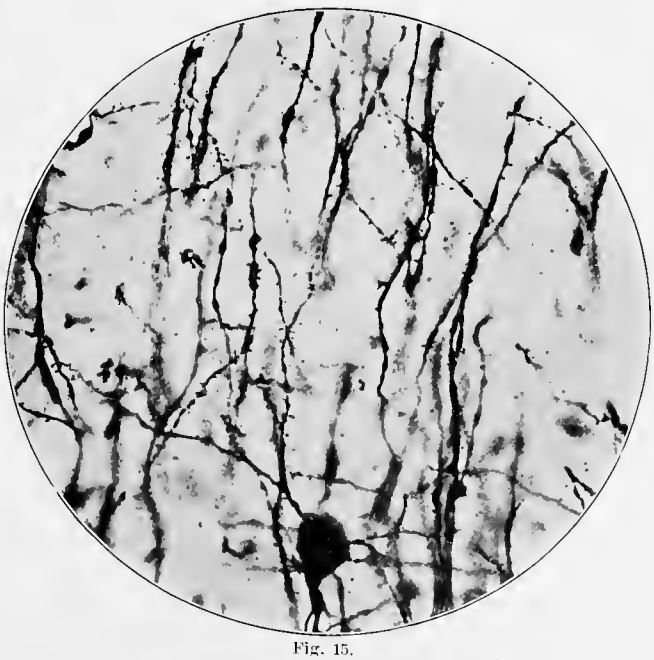

Fig. 15.

RICIN.

PHOTO. BY DR. A. G. HOEN.

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PART IV.

Lesions induced by the Action of the Toxine of Experimental Rabies on the Cortical Nerve Cell of the Rabbit's Brain.*

Studies on the pathological changes found by the silver methods in rabies are limited to the single one from the pen of Golgi (Berl. klin. Woch., No. 14, 1894). The article is a compendium of several earlier publications on the same subject, with the inclusion of the results of studies by his own silver method. After reciting the presence of certain alterations of the nerve cell as seen with other stains, principally swelling in bladder-like form, vacuole formation, and diminution of the size of the cells, then the changes found in the nucleus, including swelling, loss of the sharp outline, and changes in the chromatin particles, he proceeds to give the pathological alterations discovered in the dendrites and corpora of the cerebral nerve cells by the silver method.

"In both cell body and dendrites there are evidences of decided alterations in the form of circumscript or diffuse swelling, atrophic changes with loss of substance, a process of progressive atrophy which proceeds apparently from the cellular body to the finest extensions of the protoplasmic branches. The processes are involved to their extreme periphery. The cells lose their homogeneousness, have a granular appearance, and show diffuse swellings which give them a varicose appearance. There is also an involvement of the axis cylinder in the form of a beaded swelling of the fibre. A peculiarity of the process is that the abnormal alterations of the elements are not diffused through every portion of the central nervous system, but they are focally distributed; thus one sees zones with altered cells and others without alteration of the nerve elements."

Golgi is evidently inclined to think that the alterations above described are pathognomonic of rabies and that they are due to an inflammatory process, and gives this the name "encephalo-myelitis parenchymatosa." No mention is made in the paper of the condition of the lateral buds, and indeed they are not figured on any

*Plate XIII.

of his drawings accompanying the article, with the exception of a Purkinje cell, on which they appear to be normal.

The four adult rabbits whose cerebra formed the anatomical material for this investigation, were inoculated with bits of the central nervous system of a hydrophobic dog and a cow, after the method of trephining and inserting pieces of the tissue within the cranial cavity. Death occurred in from 12 to 18 days, and was preceded by a train of paralytic symptoms. Emaciation was not perceptible in any case. A slight degree of circumscribed proliferative lepto-meningitis was observed in all cases near the site of the inoculation.

The methods of fixing the tissues used were Müller's fluid, alcohol and formalin, but the tingeing of the sections from the last hardening agent was not equal to that from the alcohol. The staining was done with the usual Nissl, anilines, and silver phosphomolybdate methods.

Vascular System.—I have failed to discover in the cortex of the rabbits examined any evidence of coarse lesions of the vessels in the form of extensive hyperæmias, plastic exudates, and extensive emigration of corpuscular elements into the perivascular sheaths, nor could a single extravasation of the red corpuscles be found as has been described by Popoff (Virchow's Arch., Bd. 122) and others in the human subject. None of the cortical vessels of the rabbits' brains showed more than a moderate filling of the capillaries, and but a trifling emigration of the polynuclear elements, and no extravasations of plastic exudate of any description. The perivascular spaces are only moderately wide, contain a comparatively small amount of finely granular debris, no hematoidin crystals, or indeed anything beyond a few lymphoid corpuscles. The latter elements are but sparingly present in the blood within the walls of the canals. The sheaths of the vessels are not greatly altered, the endothelial nuclei are not swollen, some of the nuclei of the muscularis show a tendency to absorb less of the aniline stain than usual and show vacuoles, but the muscular fibres are not swollen or hyaline, and altogether the evidence of a degenerative process taking place in the walls of the nutrient vessels is inconsiderable.

We have, therefore, in the present cases only the indications of

a mild infection, of sufficient intensity, it is true, to cause death after the lapse of a considerable number of days, but insufficient to produce any considerable morbid change of the vascular walls, together with a degree of leucocytosis such as is often found when the soluble poison of bacterial source acts with a considerable degree of energy upon the blood-forming organs.

These conditions are therefore most favorable to enable one to ascertain the effect of the subtle poison from the rabies bacterium upon the nerve elements. Golgi's cases, in which he found karyomytosis of the nuclei of the vascular muscle, must have been of greater severity, and the damage to the nutrient supply have borne its part in the production of the nerve cell changes, which we are now able to exclude to a certain degree.

Alteration of the Nerve Elements found in the Nissl Preparations.—Interest in the stichochromic cells of the cortex centres not in the protoplasm, where indeed alterations are ill-defined, but in the contents of the central vesicle. In the place of the clear vesicle, holding a nucleus and a variable number of adnucleolar particles in a clear karyoplasm, we have now its contents everywhere turbid and more deeply stained than normal, the nucleolar particles showing a variety of dispositions. They are roughened and much larger than ordinary, so much so that the actual nucleolus is no longer distinguishable from them. These particles are either scattered equally through the karyoplasm or are segregated toward the central nuclear point and form figures similar to those found in chronic alcoholism, though less pronounced, as the extreme degree of roughness is no longer seen. Very few nuclei can be discovered showing the normal disposition of the chromatin particles. In a few of the largest pyramidal cells, where the lesions of the nuclei are not far advanced and the nucleolus can be determined, it has the appearance of being empty of all contents, the central portion remaining unstained, with a surrounding deeply-dyed membrane, from which numerous projections pass an infinitesimal distance toward its centre. Vacuolation of nuclei was also seen by Popoff, who figures a certain roughness of the nucleolar particles less pronounced than in the present instances.

Changes in the Nerve Elements seen with the Silver Phospho-Molybdate Method.—The lesions of the cortical cells in hydropho-

bia, as seen with this method, are on the same order as those induced by other poisons irritating to the tissues of the region, but present some slight differences from those we have already studied. The distribution of the pathological changes is very wide-spread among the cortical cells and are no longer present in groups and certain regions of the cellular layers, as is the rule with some of the weaker toxines. Everywhere in a section, the dendrites of the cells are found to be involved in the degeneration, and it is rather rare to see a cell in which all the various branches have been completely spared. The tumefactions are frequent along the stems, but are all of small size, and the portions of the dendrite intervening between the swellings are thin and have but very few of the gemmulæ still adherent to them, and of those remaining, still fewer show perfect staining. On the swellings, the lateral buds have completely disappeared, and left no trace of their former presence. A very careful search had to be made to discover any completely normal cells among the diseased ones.

But few of the corpora show distinct implication in the process of degeneration. An occasional one may be found having some erosion of its body, but these are rare. Lesions of the neuraxon in the form of beaded swellings, such as Golgi has described, appear to be infrequent, for in the series of several hundred preparations not more than half a dozen such cylinders could be found, two of which are depicted in Figs. 2 and 3. The cells attached to these nerve processes do not look more degenerate than other cells that have perfect axons, and indeed the cell from which Fig. 2 was drawn was approximately normal, excepting that the basal neurons did not stain at all. A most careful search among the finer branches of the collateral fibres, and among the terminal end-fibres from other sources failed to give evidence of any definite lesion affecting their threads, usually they are well tinged and the little terminal globule upon them is well stained and distinct.

Neuroglia alterations are likewise not definite. There is certainly no multiplication of either the star-rayed neuroglia nor of the vascular cells, but the latter may now and then show bodies and arms that may possibly be a little tumefied, but it is hardly sufficient to enable one to state that it is a distinct alteration.

The branches of the Purkinje cells show a small percentage of

swellings. Some of the knots are of considerable size and are well stained. The lateral buds are retained in part upon these swellings, while otherwise the branches show no diminution of the protoplasmic fur, in strong contrast to the projection cells of the cerebrum, evidencing that they are capable of greater resistance to the effects of this, as well as other poisons, than the cerebral elements. The other nerve elements of the cerebellum are not sufficiently frequently stained to permit one to determine with certainty whether they are abnormal or not. The neuroglia elements have the same conditions apparent in them as in the corresponding elements of the hemispheres.

This investigation departs in a number of particulars in its results from the one by Golgi. We find the degenerated cells universally present in every portion of the cortex, while he only sees them focally distributed. More important is the supposed primary involvement of the corpus of the nerve cell and afterwards the dendrites to their terminations. This is entirely contrary to the results obtained in any of these studies on the action of poisons on the nerve cell, and is against the law of degeneration of the nerve cell, for the element to die from its centre outwardly; either the lesion begins at the periphery and extends centralwards, or all the component members of the cell undergo necrosis synchronously. Golgi makes no mention of the condition of the gemmulæ on the dendrons in these atrophic conditions. It is extremely probable that his stain failed to color them at all, otherwise it is hardly possible that he should have overlooked such an important and readily distinguishable feature of cell degeneration as their shedding represents.

While it is true that the same swelling of the axis-cylinder fibre was found in this study as had been previously described, the lesion must be held to be a rare one, and not of sufficient frequency to constitute one of importance.

I can see no signs in any of the preparations of anything approaching an inflammatory process taking place in the cerebral tissues, only the indications of a purely degenerative reaction from the effect of the toxic substance produced by the bacterium of hydrophobia, essentially causing the same pathological changes as those induced by other soluble poisons when present in the circulation in sufficient quantity to disturb tissue nutrition.

PART V.

Pathological Alterations in the Nuclei and Nucleoli of the Nerve Cells from the Effects of Alcohol and Ricin Poisoning.*

Since the inception of the more modern methods of nerve-cell staining, the intimate structure of the contents of the nucleus seems to have attracted very slight attention. This is probably owing to one of two causes: either the chromophile particles and karyoplasm are seldom altered in cellular degenerations, or changes are absent except in the last stages when the protoplasm of the cell is actually disintegrating. Thus Friedman (Neurol. Centralblatt, No. 1, 1891), writing on the degenerative lesions of the ganglion cells in acute myelitis, states that both extensions and nucleus conduct themselves absolutely passively in the process of cellular necrosis; they do not die with the cell substance, but through the death of the cell substance.

Stroebe, who has quite recently made an analysis of the histology of degenerative and regenerative processes in the central nervous system (Centralb. f. allg. Path. u. path. Anat., Dec., 1895), gives the nucleus but the scantest notice. His description of the nuclear alterations gives loss of the sharply rounded contours with formation of irregular edges, loss of the definiteness of the contours, so that nucleus and protoplasm are no longer sharply differentiated, and certain changes in the nuclear substance by which there takes place a greater absorption of staining material. Variations in the position of the nucleus in the protoplasm are also to be regarded as evidences of the presence of a degenerative process.

Stroebe's analysis is largely drawn from experimental material, which, though the best of all for the purpose of basing a conclusion, is not sufficient in amount in the instances cited to be absolutely positive; and it is nevertheless the fact that in many chronic irritative diseases of the brain there are pronounced morbid changes in the nucleus of the nerve cells (*vide* these Reports, Vol. IV, No. 4, Art. Dementia).

A few weeks before the analysis of Stroebe was published, an

*Plate XV.

article by Sarbo appeared in the Neurol. Centralblatt for August, containing a study of the degenerations of the cells of the spinal cord following temporary ligature of the abdominal aorta. Lesions of the cellular protoplasm on the order of those universally found in acute softening are described, but more interesting is the condition of the nucleus. In the early stages of the alteration it is homogeneously stained, the dark nucleolus being sharply outlined; the borders of the nucleus being lost in the dull blue of the protoplasm. Later the nucleus becomes more intensely stained, progressively grows smaller, and stands out sharply from the surrounding cellular substance. In the last stadium the nucleus loses its oval form, becomes angular, grows smaller and smaller, until nothing remains but a pin-head dark-colored point in the centre of the shrunken protoplasm. Golgi (*l. c.*) also cites minor changes in the chromatin particles of the nucleus in hydrophobia, but, as they are not pronounced, considers them of little value.

In several of the articles of this series we have noted from time to time certain changes in the size and general appearance of the nucleoli of the nerve cells of the cortex, which to the best of our knowledge have not been hitherto described, and in certain of the preparations are very striking, especially in the animals poisoned with ricin and alcohol.

The staining of the nuclear structures was accomplished in a variety of ways, the Nissl methods being the most frequently used, and next in order magenta and Heidenhain's hematoxylin, sometimes with chrome-hardened, sometimes with alcohol preparations, but the nucleolar figures obtained after either fixing process were similar.

The normal nucleus of the nerve cell presents a rounded or oval figure of considerable size, with an outer membrane clearly defined, and holds near the centre one, sometimes two nucleoli of medium size. This nucleolus is smooth, rounded, definite in form, and is surrounded with numbers of fine chromatin particles of small but irregular size, some so minute as to be dust-like, others of slightly larger diameter, but none approximating the size of the nucleolus. The molecular particles of the nucleus are imbedded in a clear, unstaining substance that under normal conditions takes up none of the coloring matter, and is accordingly refractile and light colored (Fig. 1).

Among my preparations from cases of acute alcoholism there are occasional nuclei in which there is a beginning change in the contents of the nucleus. As a first step, the chromatin particles assume a coarser aspect, and the nucleolus itself looks as if it had short sprouts extending from its sides (Fig. 2), but the alterations on the whole are inconsiderable. In the more advanced form (Fig. 6), found in acute alcoholism, the nucleus has attained a somewhat greater size, the buds have extended some distance from the body of the nucleolus, are now connected with it only by lines of fine grains, and the chromatin particles are larger and more deeply stained. The karyoplasm has not become altered in staining qualities to any extent, a little more absorption of the dye is seen in very pronouncedly altered nuclei, but the absorption is not great.

Turning from the acute to the chronic forms of alcoholism we find the pathological alterations growing in intensity. The least affected cells, and these are far more numerous than in the acute cases, have a distinct departure from the typical nerve cell nucleus. The outlines do not appear to be altered in anywise, but the chromophile particles have among them a considerable number that are of unusual size and of irregular form. The nucleolus is swollen and covered by fine thickly set granules that mask its form to some extent. Later, this nucleolus grows in size (see Plate I, Fig. 2, micro-photograph), becomes very much roughened, and has numerous spurs or offsets of finely granular character, which sometimes stretch to the periphery of the nuclear membrane. The chromatin particles have mainly disappeared, as if they had been agglutinated and joined with the budding nucleolus, or had become adherent to it. The karyoplasm has now assumed a very refractile character, the molecular dust is exceedingly fine, and the particles are disposed equally through it, while in portions of the ring the absorption of the stain by the molecular matter is so slight as to produce the effect of almost perfect transparency of the nuclear substance.

The alteration of the nucleus in acute ricin poisoning is of even more pronounced character than in alcoholism, but on a somewhat different order. Equally with Heidenhain's hematoxylin and magenta, the lesions of the cellular nucleus are apparent, and no longer rest prominently on alterations of the nucleolus, but the

whole nuclear contents have undergone very decided retrogressive alterations.

The nucleus is now stained an uniform deep blue or red, as the case may be, has entirely lost its refractile properties, but is sharply differentiated from the protoplasm of the cell by the intensity of the staining. The karyoplasm does not seem to have shrunk to any extent, contains a multitude of deeply stained, extremely fine dust particles, with the karyoplasmic substance between them almost equally highly stained. Coarse molecular particles are entirely absent. The outline of the nucleus is sharply defined, but the nuclear membrane does not stand out quite so sharply under the microscope as it should. Imbedded in the nuclear substance one no longer sees the ordinary single nucleolus, but either one or several large corpuscular bodies that fill up a large portion of the ring. In cells that are apparently less diseased than others neighboring, we find three or four bodies that by reason of the greater absorption of the magenta stand out prominently from the nuclear substance (Figs. 7, 8). These chromophilic bodies are rounded or irregularly rounded, are sharply defined, and occasionally there is the appearance of a vacuole within their substance (Fig. 7). The most common form of the metamorphosis is seen in Fig. 10, where the nucleus now fills up more than one-half of the contents of the nuclear ring. Other quite familiar forms are seen in Figs. 9, 11, 13, 14, 15, 16. Fig. 12 shows a variety that is not so common. Around the large central corpuscle is a figure composed of rather coarse grains that extend in places to the periphery of the nucleus, while the balance of the karyoplasm shows nothing of the coarse granulation.

The process is certainly a very remarkable one. None of the ricin cases lived more than a comparatively few hours, and the various methods of protoplasmic staining showed the cell body to be greatly damaged in only exceptional instances; at least there was nothing comparable to the amount of destruction of the substance in cases of acute softening, nor do the lesions appear to be of the same order, for instead of shrinkage of the chromophilic nucleolus there is a considerably swollen condition. In the nuclei of the neuroglia, lying among the nerve cells, there is no evidence of mitosis, but they are very pronouncedly granular and absorb more of the coloring matter than usual. I therefore cannot look

upon these nuclear alterations as belonging to an abortive attempt at karyokinesis of the nerve cell, but only as evidences of degenerative alteration (indeed there is no good evidence of nuclear division in the adult nerve cells of mammals), and as the result of an irritation of the contents of the nucleus, which is finally to end in its death, perhaps synchronously with the necrosis of the protoplasm following entire destruction of the peripheral portions of the neuron.

It is not entirely clear in what manner the number of large corpuscular bodies arise, whether they are formed by a tumefaction of already existing nucleoli or whether they are newly formed from aggregations of metamorphosed molecular dust particles. In the guinea-pig (nearly all the figures are drawn from No. 6 of the acute ricin series) there is ordinarily but one nucleolus with a disposition that is reproduced in Fig. 1. If all the alterations in the nuclei were equivalent to those in Figs. 10 and 15 it might be considered extremely probable that one was observing simply an extreme swelling of a single nucleolus, but in others where there are several almost equally large corpuscles, we cannot suppose, or at least there is no warrant for the supposition, that all these bodies have arisen by a process of budding from a single nucleolus. On the other hand the highly tinged masses are found in the several quarters of the nuclear field; and occasionally, as in Figs. 11 and 14, it would seem as if several of these had come together and formed the enlarged masses. It is therefore more probable that the nucleolar bodies are formed, owing to the peculiar effect of the ricin on the cellular structures, from the nuclear molecular particles aggregating together and fusing, leaving the nuclear substance free from molecular particles, but leaving it also changed in properties, as is evidenced by the greater absorption of the dye.

In these changes the proper nucleolus plays the same part as one of the smaller molecular chromophilic particles, fusing with the smaller ones that approach it. In these changes within the nuclear structures there is evidence of smaller or greater movement among its contents going on at all times.

All the lesions of the nerve cell in chronic toxæmias are most probably part of the same condition, an irritative destruction of the cell from the combined effects of the toxine and shutting off of a healthy nutrient supply.

II.

THE INTRA-CEREBRAL NERVE-FIBRE TERMINAL-APPARATUS, AND MODES OF TRANSMISSION OF NERVOUS IMPULSES.*

The exact histological appearance of the end-apparatus of the intra-cerebral nerve fibres does not seem to have been determined and described with the clearness of detail that has followed the application of the silver methods to some other portions of the neuron.

Lenhossék (Feinere Bau des Nervensysts. 1895), writing at a late date, speaks of the *free pointed endings to the nerve fibres.* Even the great Spanish investigator, Cajal, in his "Nouvelle Ideas du System Nerveux, 1895," is not quite so clear on this point as he usually is when he writes that the ascending fibres of the cortex, which have a vertical or oblique course through the medullary layers, have their points of contact with the protoplasm of the dendritic structures in the intervals between the short transverse processes (gemmulæ), around which the ascending fibres twine; and entirely ignores the thought that the lateral buds can have any function in this act of transmission. Such a discharge of the nerve forces from cell to cell taking place at hundreds of indefinite points could not fail to produce stimuli that would be more often aberrant than direct, and in all likelihood such an arrangement would produce the utmost confusion of thought and motion, a veritable incoordination of the cerebral functions, which would reduce direct cerebration to a nullity.

Cajal is by no means unfamiliar with the true ending of the nervous end-apparatus, for a few pages further on in the same book, in his description of the mode of ending of the collaterals of the great pyramidal cells, he describes their finest branches as terminating freely by means of a nodosity. Furthermore, he figures in his plates all the free endings terminating in a similar manner, be they collaterals, terminal branches from the projection cells, or the ramifying ones from the intermediary.

It would appear that the Spanish savant had overlooked one important factor, when he takes for granted that the finer ramuscules of the nerve fibres are unprotected by any insulating cover-

*Plate XV.

ing. The researches of Flechsig, as well as my own, have shown that these fine branches are furnished with a thin layer of myeline nearly to their terminations, and beyond this medullary covering there is apparently a protective sheath of great tenuity not easily recognized by ordinary methods of staining, which the silver method does not show at all. It is therefore more than probable that it is only at the free bulbous termination of the nerve filaments that we have naked protoplasm, and from this uncovered nervous substance the dynamic forces, generated in the corpora of the nerve cells, are discharged, though contiguity, onto the protoplasmic substance of other cells.

Thus in contradistinction to the hypothesis of Cajal we have only comparatively few points at which the nervous forces may discharge themselves from axons to the protoplasm of other cells, and these are seated at definite points on the terminal arborizations of the nerve filaments; for otherwise what would be the necessity of a terminal apparatus were the nerve conductors free to discharge their dynamic forces at any point at which they came into contact with the substance of a dendron? The very closely interlacing feltwork of dendrite and axon, especially in the outermost layer of the cortex, would alone necessitate some protective arrangement, for situated as the cells and fibres are, most closely packed together, nay in fact at times touching each other, the constant overflow of stimuli from cell to cell would be almost continuous.

Granting that the ultimate fibrillæ of the axons have a protective covering, we have still the protoplasm of the dendritic twigs that are unprotected from possible aberrant nerve excitations from the end-apparatus. But is this strictly true? Around the body of the cell we find an insulating mass of fluid contained in the pericellular lymph sac, and as a capsule to the sac there appears a slight condensation of the tissue at this point that would take the place of a retaining membrane. This membrane apparently terminates where the first of the gemmulæ are thrown off from the ascending portion of the primordial process, and likewise at the location where the first buds appear on the basal dendrites. Does the insulating fluid and covering really end at this point? In absolute alcohol sections of the cortex of the cerebellum, taken

parallel with the surface and stained with the anilines, particularly the blue-black, it is quite readily demonstrable that the thin membrane, which is now undoubtedly composed of fine glia filaments, does not really cease at this point, but becomes attenuated, and continues to ascend and cover the protoplasmic prolongations of the cell. It would seem from this arrangement as if it were probable that the cells of the cortex are likewise furnished with an enveloping membrane. We consider, therefore, that the very fine stem of the gemmule, at the point of branching from the dendritic stem, penetrates through this enveloping sheath, and it is, accordingly, only at the tips of the gemmules that we actually have free dendritic protoplasm. Thus it is only at the nearest point at which it is conceivable for the impulse from the end-ramuscules of the nerve fibre to come into contiguity with the free cellular protoplasm that we find uncovered cellular substance.

This theory is in entire concordance with the anatomical structures of the parts, and accounts for the fact that the twigs of the dendrites and the fibres touch each other frequently, and in a manner that appears to be perfectly indifferent for the different kinds of nervous substance, receptive and projective.

The silver phospho-molybdate method usually stains with great distinctness the end-apparatus of the nerve fibres which have their origin both intrinsic and extrinsic to the cortex, the only ones that are insufficiently impregnated are those belonging to the peculiar cells of the molecular layer. So far as the end-apparatus of the collaterals from the psychical cells is concerned, the terminations of the intermediary cells, the fibres entering from the medullated masses, all have the same end-apparatus, which consists solely of a simple, freely terminating bulbous ending, situated upon the extremity of the finest branches of the nerve fibres (Figs. 1, 2).

With the collaterals of the pyramidal cells and the axons of the intermediary, particularly the pluripolar ones, this method of terminating can very distinctly and definitely be determined. With the terminations of the association fibres it is equally distinct, but the difficulties of ascertaining to which class the fibre belongs are greatly increased by the length of the trajecture through the layers of the brain-rind, and indeed were it not for certain characteristic differences between the terminal apparatus of intrinsic and

extrinsic fibres it would be most difficult to determine where the latter belonged, as it is almost impossible to follow the extrinsic fibres, owing to their sinuosities and length, through the entire thickness of the cortex.

These differences between the two kinds of fibres consist entirely in the final disposition of the terminal ramifications of the collaterals from the association, ascending fibres, and those from the axons of the psychical and other local cells.

The arrangement pursued by the first series is to break up into a number of filaments, usually at some distance from one another, and then these filaments redivide into a small number of others coursing over comparatively a short extent of territory, each terminal filament bearing upon its extremity a globular or flattened bulb. The number of these bulbs upon each terminal branch of the association and ascending fibres from the inferior regions is not numerous, seldom exceeding six or eight, and the form is that of an arborization of the nerve twig (Fig. 2).

On the other hand, the terminations from the collaterals of the psychical cells are much more numerous on the final branches and show a very different disposition. The collaterals winding among the dendrites of the cells, ofttimes closely applied to them and twisting in and out between the gemmulæ, seldom show any definite endings until the mid-portion of the layer of small pyramidal cells is reached (Fig. 1). There they split up into a number of exceedingly fine branches, running frequently parallel with the course pursued by the apical and basal dendrites, and eventually give off, at frequent intervals, exceedingly short collaterals, which ordinarily only come off from the parent stem on the side toward the nearest dendritic process. Each of the short terminal ramuscules ends in a bulb of precisely similar form to those upon the branches of the ascending fibres, that is either rounded or biscuit shaped, and these spherical apparatus are closely adjusted against the bulbous tips of the gemmules, at times the approximation being so close that the impression is given of actual contact, though it should be remembered that the slightest overlapping will produce the same effect, and on the whole it is more probable that there is no actual contact, but that the axonal discharges of the stimuli overleap the infinitesimal distance between bulb and gemmule.

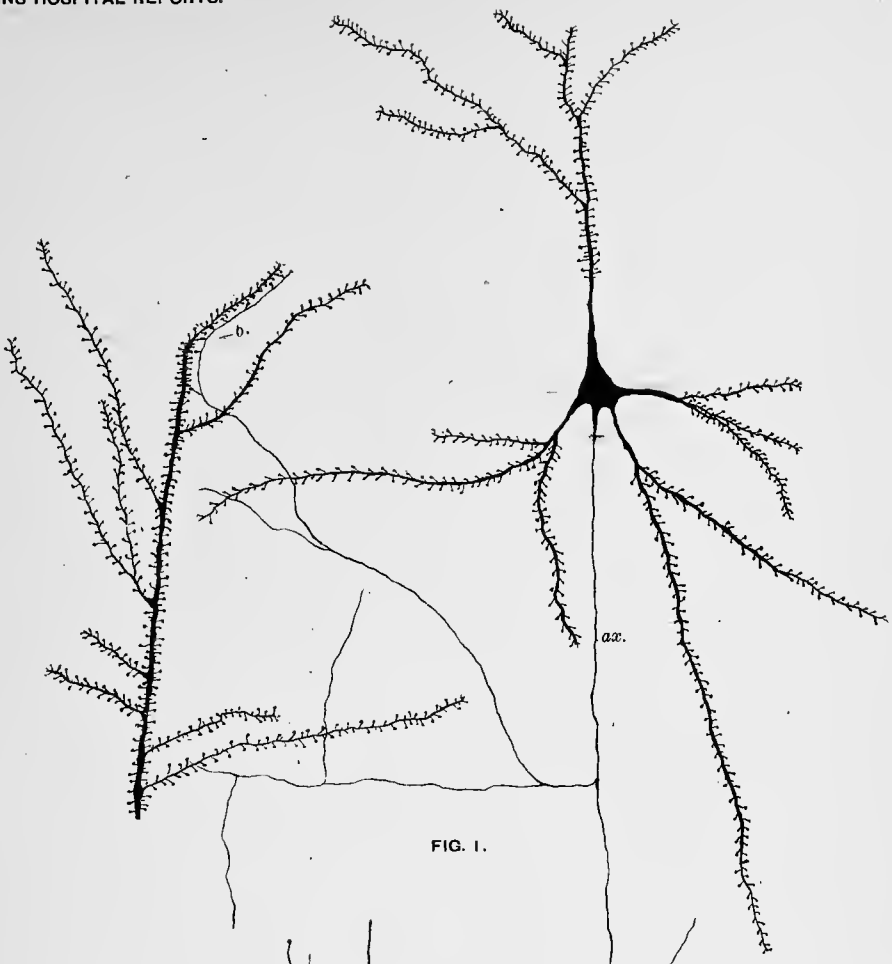

FIG. 1.

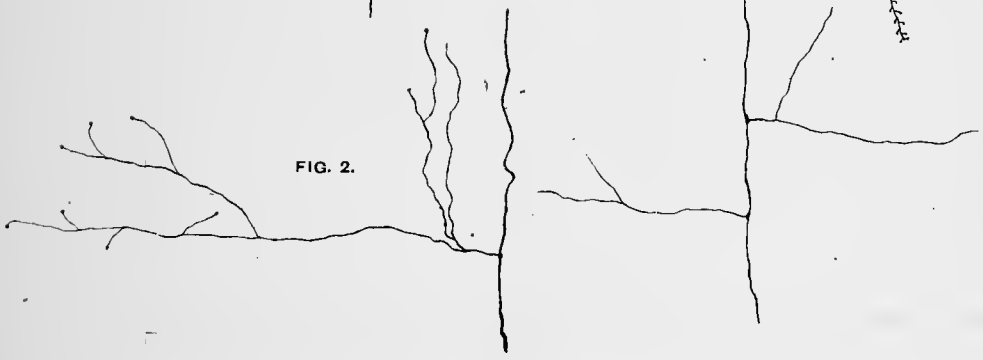

FIG. 2.

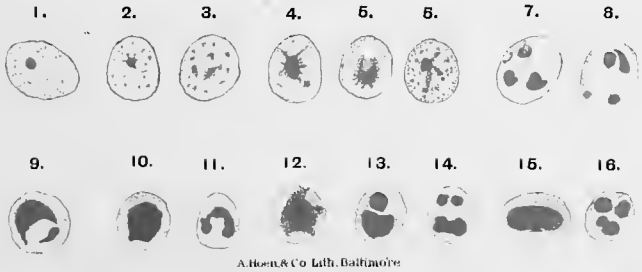

FIG. 3.

A. Hoen & Co. Lith. Baltimore

NERVE ENDINGS AND NUCLEAR CHANGES.

HUMAN PSYCHICAL CELLS WITH AXON.

The interpretation of the objective existence of the terminal apparatus of the nerve fibres cannot be made but in one way, namely, that the impressions conveyed from external sources to central cell, and from local cell to local cell, is not accomplished by a diffusion of the excitation through the whole cortex, or even at various points along the course of the finer branches of the axons, but at single points, perfectly definite in their distribution, and that these points are situated only at the extremities of the nerve fibre twigs, in the form of an histologically exact formation —the bulbous ending of the nerve fibre—which in itself constitutes the sole and only means for the carrying over of the cellular forces from axon to dendron, and from cell to cell, and is in entire conformity with the conception of Waldeyer of the entity of the neuron, each cell standing as an unit in the nervous formation, and only in continuity with others at definite points.

Explanation of the Drawings.

Fig. 1. Psychical neuron, showing the end-apparatus of a collateral situated against the dendrite of another cell. Human.

Fig. 2. Form of termination of the ascending fibres of the cortex. Guinea-pig.

In 1870, Wilks (1), of Guy's Hospital, in the Reports for that year, described a case of lethal bulbar paralysis occurring in a young girl that had been admitted to the institution for general weakness, difficulty in speech, and strabismus, and later implication of the respiratory and deglutitory movements. The microscopic examination of the medulla showed nothing abnormal.

In the year 1879, Erb (2) called the attention of neurologists to an apparently new bulbar symptom-complex, characterized by ptosis, weakness of the neck muscles, paresis of the muscles of mastication, disturbance of the action of the muscles in the upper facial territory, and weakness of the extremities; presenting the clinical histories of three cases of the disease, unaccompanied by any report of autopsies.

A period of seven years now elapsed before any similar case was described. Then Oppenheim, in Virchow's Archives (3), published an account of a parallel case occurring in a twenty-nine-year-old woman, death taking place in an attack of dyspnœa.

In the same year Eisenlohr (4) brought forward another case, and these were followed in the next few years with others by Shaw (5), Jolly (6), Goldflam (7), Hoppe (8), Bernhardt (9), Remak (10), Strümpell (11), Pineles (12), and Murri (13). The total number to the present date is twenty-one well authenticated clinical cases, with six autopsies, all of which were absolutely negative as far as degeneration of the bulbar nuclei and cortical cells was concerned.

To these twenty-one cases are to be added four others in which some portion of the symptom-complex was present, but which deviate from the more numerous ones in important details. These are the fourth case of Pineles (14), in which the symptoms followed an attack of typhoid fever, and in which it is reasonable to suppose there were organic lesions; the case of Senator (15), in which there was well-marked hemiplegia; Mayer's case (16), where the microscopic examination showed degeneration of the root-fibres, but no lesion of the nuclei on the floor of the fourth ventricle; and

Raymond's (17), which included paresis of the inferior facial, hypoglossus, motor trigeminus, abducens, and oculo-motor, but was not quite symmetrical.

Clinically, since Erb's first description, the symptoms of the trouble have been considerably extended, and now the cardinal signs are to be found in disturbances in the territory of all the cephalic nerves, principally those appertaining to speech and deglutition, weakness of the muscles of mastication, a medium degree of ptosis, then paresis of the extremities, and abnormally early muscular exhaustion. Disturbances in the domain of the optic, olfactory, auditory, and degustatory nerves do not seem hitherto to have been recorded. Ordinary skin and muscular sensations do not appear to have been found to be impaired.

The disease does not always have a fatal issue, indeed Goldflam presented his cases under the title of an "Apparently Curable Form of Bulbar Paralysis," and several other writers have had cases to apparently recover, though it is true some of them afterwards relapsed.

I now present to your notice the history of the twenty-second case of what Strümpell has lately, from the most striking symptom, called "Asthenic Bulbar Paralysis," which, to my knowledge, is the first recorded case in America that has come to the autopsy table.

C—— K——, a German-American, age 28, was admitted to the Hospital Department of the City Asylum in August, 1892, for "paresis affecting the ocular and facial muscles." Family history: The general previous and family history were given by an older sister of the patient, a strong, healthy woman, for her class well educated and intelligent. The grandparents both lived to about the age of seventy-five years, were generally healthy, and suffered from no troubles of a nervous nature. The father of the patient, a cooper by trade, died at the age of fifty-six years from cancer of the stomach. Up to the time of his last illness he always enjoyed good health. The mother of K—— is living, sixty-six years of age, is in good health, but is not over-intelligent. Besides the patient there are three sisters in the family, living and in good health. An older brother died some years ago of lung trouble induced by a severe wetting, which was followed by pneu-

monia, and later by tubercular disease. Several younger children in the family died of common children's maladies. There is no history of miscarriages on the mother's part.

K—— was born naturally. At the age of eighteen months he had a severe attack of variola, later there was a slight illness from measles, also a few minor sicknesses. He was sent to a German school at the age of seven years, and is reported by his sister to have learnt very slowly and was very apt to forget all he had learnt. When fourteen years old he was taken from school and set to work in his father's cooper-shop. There he attracted attention principally by the slowness of his movements, as the sister described it, "when he stooped he seemed never to be able to get up again." On several occasions he excited his father's ire by this slowness, and soon afterwards was apprenticed to a blacksmith. In this position he did not succeed much better, and during the following three years he alternated between the cooper-shop, blacksmithy, and selling papers on the street.

At the age of twenty-one the first apparent symptoms of the present malady manifested themselves. The sister noticed that his legs were insecure under him, he became easily tired, and in walking up and down the steps he was liable to trip and fall, also that he was becoming rather somnolent. On coming home in the evening he would retire immediately, and "remained in the same position in bed all night and until he was aroused in the morning."

An inordinate increase of appetite about the same time attracted attention, together with extreme difficulty in handling his knife and fork. No vertigo, unsteadiness in standing, double vision or headache were then or afterwards complained of or noted, nor was any considerable trouble in swallowing food apparent.

During the twenty-second and twenty-third years no further symptoms were noticed. In the twenty-fourth a new series commenced. Vomiting, usually after meals, now began and continued over a period of three or four months, then ceased absolutely, and did not recur. Soon after this a very pronounced deafness came on, lasted for some months and then subsided to a degree. There was no running from the ears, or other evidence of middle-ear trouble, to account for the hardness of hearing. Keenness of the sense of hearing has never been completely restored.

The clumsiness in the gait now increased markedly, and though the patient was able to walk considerable distances, he always seemed exhausted on reaching home and went directly to bed. Mental apathy now became well marked, K—— sitting for hours in the same position, taking no interest in anything, and entirely negligent as to personal cleanliness. Work in the blacksmithy was now abandoned for selling newspapers and visiting dispensaries.

Soon after his speech became markedly affected, so much so that those around him could no longer understand his utterances, even when limited to a very few words. This difficulty in articulation came on gradually, but was complete within a few months. Slowly and little by little he regained the ability to utter a few words with sufficient distinctness to make himself understood in an imperfect way.

During the twenty-sixth year there were no new symptoms, only the general weakness increased to a more distinct paresis.

In the twenty-seventh year the eyeballs became "stiff" and fixed, and a moderate double falling of the eyelids developed by degrees. The fixation of the eyeballs occurred some time before the drooping of the lids, and the dilated pupils and fixed staring gaze, together with a certain falling of the cheeks, gave K—— a very peculiar appearance, further heightened at the time by a livid-blue œdema of the cutaneous tissues around the eye.

Syphilis and alcoholism are absolutely denied, and there is no history of a fall or blow on the head. There are neither marks of syphilis, congenital or acquired, nor scars from wounds on the head.

In 1890, K—— entered the dispensary of the Johns Hopkins Hospital, and the notes made at that time are abstracted in so far as they immediately concern the condition of our patient. "K—— is clumsy in his motions, hard of hearing, and has a stuttering speech. All these symptoms are said to be much better now than a few months ago. He has, however, been growing weaker. The arms and legs jerk and contract. There is dull pain in the legs. There is no headache and no trouble with the bladder or rectum. There has been no double vision. At times the hands become white and dead-looking; there are also white areas about the eyes and chin.

A note of June 9, giving his present state, adds: The patient is dull and sleepy looking. He is mentally slow. The voice is thick. The speech is stuttering. Pronounces all his letters distinctly. Pupils are equal and react to light. The eyeballs can be turned inwardly and downwardly, but not upwardly. They are steady. There is no ptosis. The fundus of the eye shows nothing abnormal. Vision 20/20. The muscles of the face act slowly to the will and there is some tremor. The tongue is protruded straight. Sensation about the face seems to be normal.

The hands and arms are moved slowly and clumsily. Muscular strength is subnormal. The deep reflexes are exaggerated. Cutaneous sensation is normal. The walk is unsteady and the patient appears weak. There is no contracture of the legs. The muscular strength is below normal, but better than in the arms. Ankle clonus, three or four jerks. There is no ataxia.

Present state, September, 1892.—K—— is a rather tall, heavily built man, weighing 170 pounds. The tissues are well nourished, the bony framework is heavy, muscles large and moderately developed.

The skull is brachycephalic, fifty-five cm. in circumference and without any marked irregularities in contour, though the arch is a little low.

The facial expression is dull, heavy, the cheeks are drooping, the naso-labial folds obliterated, the eyes habitually half-closed, and the lids and surrounding skin have a peculiar livid-white œdematous appearance. The patient throws his head backward to permit of vision, and then a fixed staring expression about the eyeballs is noticeable. The pupils are even, widely dilated, and there is neither nystagmus nor squinting. K—— sits usually with the head bowed forward, apparently on account of the weakness of the neck muscles.

Coarse muscular strength in the hands is almost absent, the dynamometer only moving to fifty kilos with the utmost effort. The neck muscles have about the same degree of feebleness as the hands. The legs are even more paretic, only with difficulty can he move a few paces at a time, and there is great liability to fall forward at any moment. He stands upright with great uncertainty on account of the muscular weakness, but there is absolutely

no ataxia with either coarse or fine movements. Coarse muscular movements, like repeatedly grasping a stick, are fairly well performed when the motions are first begun, but quickly the muscles exhaust and it becomes impossible for him to grasp the rod. There are no local or general muscular atrophies or hypertrophies.

The deep reflexes are considerably exaggerated, the knee jerk has several beats, and a slight ankle clonus may be produced at pleasure. Mechanical irritations of the skin produce normal reactions. The reaction of all the muscles of the trunk and extremities to faradism is normal, except for the tendency to early exhaustion. There are no fibrillary twitchings.

The sensory qualities—heat, cold, tactile perceptions, pressure, position—seem to be absolutely normal. No neuralgic pains are complained of by the patient.

The heart sounds are irregular, there is no distinct murmur, the pulse wave is slightly uneven, and the beats number 120 to the minute. The respiratory movements do not seem to be disturbed.

The vegetative functions are normal. The urine contains neither sugar nor albumen. The internal organs are healthy.

With the exception of the sensory V and the ocular nerves, the special senses and functions of all the cranial nerves seem to be impaired in greater or less degree.

There is absolute bilateral anosmia, with no defect from interrupted inspiration or expiration. Volatile oils, camphor, smelling salts, etc., are unperceived and unrecognized. There is slight withdrawal of the head when a bottle of strong ammonia is approached closely to the nostrils, also the head is withdrawn when the nose is titillated.

Vision does not seem to be disturbed. Patient has forgotten the little education he had and spells letter by letter ordinary brevier type at the distance of 45 cm., provided the book is in his lap or the eyelids are raised for him, so that the drooping of the lids will not interfere with vision. Further off the spelling is accomplished with greater difficulty. The pupils are in a state of mid-dilatation and do not respond either to light or accommodation. There is no exophthalmos. An ophthalmoscopic examination of the fundus of the eye failed to demonstrate anything abnormal. The conjunctival reflex is present. The field of vision, obtained

after great patience and perseverance, is given in the accom-
ing diagrams. White and blue have about the same field.
's are recognized, even to a difference between shades of the
color.

ere is incomplete duplex ptosis, the edge of the eyelids fall-
ust to the edge of the pupil when the head is vertical and
ring the member to be thrown backward when distinct vision
ired. When an examination is begun K—— can raise the
ls three or four times in succession, then the muscles become
ısted and do not react to the will.

ere is paresis of the internal, external, inferior, and oblique
les of both eyes, the balls being practically immovable, except
slight ability to roll them upward. An unusual symptom in
ence to the movements of the eyeballs is noticeable. When
ead is rotated either to the right or left the eyeballs do not
v the movements of the head, but remain stationary. Stell-
symptom is very noticeable. The degree of immobility of
yeballs varies considerably from day to day, sometimes they
ompletely fixed, while at others the movements are freer.

e disturbance in the motor division of the trigeminus is not
eat as in the domain of the oculo-motor nerves, the muscles of
cation responding naturally to the will, but are soon exhausted,
a few mouthfuls being taken at meals before eating becomes
ious and has to be discontinued for the time, to be begun
in a few moments. Early exhaustion of the masseters to the
ic current is well marked.

nsation seems to be well preserved within all portions of the
bution of the V nerves.

e functions of the muscles of expression supplied by the
th nerve are in partial abeyance, and respond imperfectly to
vill. The forehead is smooth, is never furrowed during an
to remember or in speaking. The orbicular muscles do not
nd strongly. Puckering of the mouth is performed with
ulty, while whistling is impossible. The facial muscles in
al respond too readily to faradism and exhaust quickly.
pronunciation of the labials is difficult, but one can under-
that they are correctly given. All letters of the alphabet
qually bady enunciated. There is no drooling of the saliva

from the corners of the mouth, on the contrary, the orbicularis oris can close the lips quite firmly, and it would seem that certain fibres of the muscle were more feeble than others.

Patient is somewhat deaf to ordinary sounds and the voice. A rather loud ticking watch is heard at a distance of 28 cm., but further off its sound is not heard. An examination of the external ear and drum shows nothing unusual.

Tactile perceptions in the area of distribution of the glosso-pharyngeal are but very slightly, if at all, obtunded, but it is difficult to decide if the finer tests are felt, owing to the patient's mental dullness. The palate hangs low toward the floor of the mouth, and the arches are flattened. There is a well-defined palatal and pharyngeal reflex.

Articulation, apart from the pronunciation of the labials and linguals, is badly performed and scarcely to be understood at all, even to the shortest sentences. No laryngeal examination was made.

The motor functions of the muscles of the tongue are defective, the organ cannot be protruded over the edge of the teeth, and is pale, flabby, but not in the least atrophic.

The only perceptible involvement of the pneumogastric lies in an irregular action of the heart and the tachycardia (120 beats). Equal irregularity is shown by the pulse wave.

A special examination of the gustatory functions gave the following result: Everything placed in the mouth is called salt, sugar is salt, salt is salt. Bitter, as quinine, placed on the tongue, even in concentrated acid solution, is apparently unperceived and certainly causes no annoyance. Acids give equally negative results. Electric gustatory sensations are certainly more acute over the anterior two-thirds of the tongue than over the posterior third. Three cells of a weak Barrett battery produce a perceptible sensation in the anterior portions, while in the posterior regions five cells are required, and the same number give a perceptible sensation over the hard palate and palatine arches.

The mental condition of the patient is one of calm content, he always feels well, is never depressed, and there are no delusions of any kind. The appetite is ravenous, food of any kind being acceptable. K—— is a shameless masturbator and practices the

on every occasion. Iodines and iron were tried without
; in the way of improvement.
tober 12, 1892.—There is some slight improvement in the
ı of the eyeball muscles. He is now able to rotate the balls
e eyes to a limited extent. Otherwise his condition remains
anged.
nuary, 1893.—Patient has been several times examined.
ondition has remained unchanged, except that he is weaker
the eyeballs are more fixed. Mastication is less easily per-
ed than a year ago.
ırch, 1895.—There is no apparent change in K——'s condi-
since the last note was taken. There have never been any-
approaching hysterical symptoms nor vaso-motor disturb-

ly 13, 1895.—To-day while being fed with a soup he sud-
choked, and before assistance could be rendered, asphyx-
and died. There had been no previous attacks of dyspnœa.
ıtopsy, July 14, 1895.—Cadaver of a well-nourished man
ut any abnormalities. Viscera, both thoracic and abdominal,
hy. On examining the throat a mass of meat was found
d in the upper part of the pharynx, suffocation being there-
he direct cause of death. The brain was removed from the
al cavity and preserved in 5% formaldehyde solution until
letely hardened and then cut. The hard and soft mem-
s were healthy. The encephalon with the soft membranes
ıed about 1200 grammes.
croscopic Examination of the Brain.—The blood-vessels at
ase and in the great fissures are healthy. The conformation
e convolutions is very simple. The depth of the sulci is not
There are no abnormalities in either convolutions or fis-
on the external aspect of the hemispheres, except that the
lutions of the occipital lobe of the left hemisphere run hori-
lly instead of vertically, and are divided into four instead of
convolutions. The occipital convolutions of the opposite
onform to the usual arrangement.
the internal aspect of the same (left) hemisphere the cuneus
imentary, and its gray tissues are confluent with those of the
al lobe, the calcarine fissure being absent through its entire

length. The remaining portions of the inner aspect of this hemisphere conform to the usual conformation.

In the right hemisphere there is no departure from the usual arrangement of the internal aspect, though the cuneus appears somewhat small for the size of the brain, but the calcarine fissure is well marked and separates it thoroughly from the lingual lobe.

There are nowhere any pits or depressions on the surface of the cortex indicating local atrophies of the cerebral substance.

The cerebellum is small, does not cover the inferior aspect of the occipital lobes, and is somewhat grayer than ordinary in color. The pons Varoli is likewise small, especially in the bridge of the crossing cerebellar fibres. The medulla appears by contrast with the pons large, the pyramids are large and distinctly marked, the restiform bodies are well developed. There are no traces of descending degeneration in the lateral columns of the upper cervical cord.

On the posterior surface of the medulla, the ependyma covering the ventricle is a little roughened and has evidently been congested. At the level of the striæ acusticæ the two pits are unusually deep. The left is somewhat deeper than the right. The iter is patulous and quite large, but there is no evidence of compression of the tissues from fluid. On section the medulla appears quite normal.

The hemispheres were cut after the manner of Pitres. The right was absolutely normal, not even a spot of punctate hemorrhage being found. In the left, at a point commencing 4 cm. back of the tip of the anterior pole of the lobe and beneath the foot of the second frontal convolution, is an irregular cavity nearly 3 cm. in average width by 3 cm. in length, so situated as to intersect the anterior callosal fibres passing from this hemisphere to the opposite side. The end of the cavity posteriorly is just at the anterior margin of the anterior central gyrus, hardly passing under it at all. The middle and posterior fibres of the corpus callosum do not seem to have been influenced by the lesion. The lateral ventricle is separated from the defect by one-half centimetre of white matter, and outwardly the convolutions show no depression above it.

Microscopic Examination.—The entire bulb, with portions of

the central gyri and cerebellum, were removed from the brain, part being for further treatment immersed in 95% alcohol, and part in Müller's fluid. The staining was accomplished with eosin-hematoxylin, Nissl's magenta, Weigert's hematoxylin, and the silver phospho-molybdate method.

Medulla and Pons.—The entire bulb, from the end of the decussation of the pyramids through the cephalic end of the iter, was laid off in divisions, and every fifth section taken and stained. The cells of all the nuclei on the floor of the ventricle, the scattered gray masses more centrally situated, the ganglionic bodies of the olives, all appeared perfectly normal; their cells were numerous, the processes well stained and strong, with nothing unusual discernible in the nuclei or nucleoli.

Particular attention was given to the nuclei of the III nerves, but the only variation I could find was that their nerve cells appeared rather more numerous and thickly set together than is customary. No bands of medullated fibres showed under the Weigert treatment any traces of degeneration, the pyramidal tracts being well developed and the root fibres not showing even an undue degree of varicosity of their medullary sheaths.

In the Nissl preparations, owing to the formol fixation, the chromatin structures in the protoplasm of the nerve cells did not come out with the customary distinctness, but they were otherwise well stained, with numerous long prolongations showing occasional striæ. Not a diseased blood-vessel could be found anywhere in the bulb.

The cerebellar tissues were in every respect healthy.

Cerebrum.—A number of sections were made from the walls of the cavity in the left frontal region and stained with hematoxylin-eosin and with Weigert. The wall of the defect was very thin, and was encrusted with small deposits of hematoidin crystals and debris. The surrounding structures showed very little damage.

The silver sections, made from the central gyri, were very defective, only areas here and there receiving the impregnation. The staining of single cells, however, was good. The cell bodies, dendrites, and axons, were fairly well developed, but the gemmulæ upon the dendrons showed a very interesting condition. They were

ry long, sparsely set upon the stems, but were not otherwise normal. The condition is probably one of retarded develop-nt.

Hematoxylin-eosin staining showed the cortical cells to be merous, and the bodies, nuclei, and nucleoli normal. No vas-ar lesions were discovered.

From the clinical history we see a progressive but very slow velopment of the malady. The patient, who had always been ntally inapt, acquires in his twenty-first year a decided awk-rdness and inability to freely use the extremities. Shortly erwards there is a disturbance in the domain of the vago-essorius nerves, succeeded soon by a deafness of a very pro-unced character. An increase of the mental disability is now led to the symptom-complex, and on his admission to the hos-al there is deep mental reduction, which is permanent.

Disturbance of the speech faculties follows next in the symptom ies, but this is not from the mental reduction, but from weak-s of the muscles concerned in articulation and phonation. The ech defect was comparatively slow in reaching its acme, but re remarkable was a partial return of the faculty, sufficient to able the patient to make his wants understood.

Next in succession came the oculo-motor paresis, which con-uted the closest approach to an actual paralysis of any of the poreal muscles, and for many weeks at a time extended to an ost absolute abeyance of the movements of the eyeballs. After involvement of the III, IV and VI nerves we find a slowly veloping incomplete double ptosis, and to a certain degree iritic akness, which, however, occurred previous to the beginning of ptosis. Chiefly remarkable among the many symptoms was tendency of all the voluntary muscles toward quick exhaustion, h to the mental effort and to electricity, though this symptom equally met with in other diseases, notably, Graves. A ten-ncy toward change in the degree of the paretic symptoms was o a notable feature, the patient appearing much better at one ne than at another.

The functions of all the cerebro-spinal nerves were found defi-nt, with considerable variation in the amount of the weakness.

No local atrophies or hypertrophies were ever discovered. A number of the organs of special sense were also found deficient in their functions. Uninvolved remained only the nerves of cutaneous sensation, and the functions of the optic nerves.

We find in the present case three departures from the symptom-array mentioned in the other twenty-one, namely, mental obtundity, involvement of certain of the special senses, and an almost complete ophthalmoplegia, interna and externa.

At the section of the encephalon a comparatively small defect was found located at a point at which it intersected some of the callosal fibres. The date of the occurrence of the cerebral hemorrhage that caused the cavity is extremely uncertain, in all likelihood it took place in the first few years of life. Perhaps, the attack of variola at the age of eighteen months may have been the etiological factor. We must consider this cavity, situated in a most important region of the brain, as the cause of the inactive mental condition noticed by the relatives, and see in it a sufficient one. But with all the hindrances there was still sufficient mental development to enable K—— to learn to read, and, to a limited extent, write, and it was not until the twenty-fourth year that he showed an active degree of retrograde mentation. From the standpoint of his family, he now became demented and a care and hindrance to the rest of the household, as he was now no longer a bread-winner, as he had been before.

It would seem, therefore, that some process, synchronous with the bulbo-spinal symptoms, took place in the cells of the cortex, changes that the microscopic examination leave in the most complete darkness, as they only show a retardation in the development of the cellular structures, but no degenerative lesions.

The involvement of certain of the special senses is, perhaps, not the least interesting aspect of the case. I have been unable to find any mention of a similar state in any of the described cases, and can only regard it as a portion of the general symptom-complex of the disease, and one which allies it to certain cases of sensory anæsthesia, as has been described by von Ziemssen (18).

Paralysis of the ocular muscles is not totally unknown in asthenic bulbar paralysis, for in the first case recorded by Wilks there is mention of a distinct strabismus, and in one of Goldflam's

; there was an almost total ophthalmoplegia externa. Still
ı the absence of this symptom in many other examples it must
ıe of comparative rarity, this being the first case in which there
)een involvement of all the ocular muscles, including those of
ris. Ptosis is present in the majority of the examples.
he case seems to overlap the dividing line between several
dies of equally uncertain nature—sensory anæsthesia and cer-
form of duplex ophthalmoplegia, also to trench strongly upon
m of progressive dementia that occurs in young persons, which
:ompanied by general muscular weakness with increase of
leep reflexes. That it belongs to the category of bulbar para-
without anatomical lesion the microscopic examination is
ient evidence.
he slowness of the development of the disease in K—— is
what unusual, though not unprecedented (Murri, *l. c.*), but
he other hand the majority of the examples have been much
rapid, some of the cases running through the symptom-com-
and recovering within a period of six months (*vide* Goldflam,

ge and sex have no dominating influence, cases being reported
ı nine to fifteen years, and the division among the sexes is
ly equal. It may begin in a great variety of ways, now in
cranial nerves, now in the extremities, but always slowly.
h occurs usually from suffocation, either after repeated attacks
spnœa or during the ingestion of food. The etiology is entirely
ıded in mystery, as is its anatomical location, whether in the
o-spinal or cortical centres.

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